BRAIN

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A Journal of Neurology

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BRAIN.

PART 1, VOL. 61.

INCREASED SPONTANEOUS ACTIVITY PRODUCED IN MONKEYS BY BRAIN LESIONS.

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THE rôle played by the frontal lobes in the regulation and control of spontaneous activity is still a subject of dispute. Ferrier (1876), Bianchi (1922), Lashley (1920), Jacobsen (1931 and 1936), and Levin (1936), found that removal of the frontal lobes in animals (dogs, monkeys and rats) resulted in restlessness and increased activity, while Goldstein (1927) and Kleist (1934) reported that destruction of the frontal lobes in man by tumours or war injuries resulted in apathy and decreased activity. Brickner (1934) reported increased restlessness in a patient with surgical removal of both frontal lobes.

All these experimental and clinical observations were made incidentally to other studies and were handicapped by the lack of adequate means of measuring activity. The clinical work was further handicapped by the lack of definite knowledge regarding the exact localization of the lesions.

These limitations have been overcome, at least in large part, in the following experiments in which the effects produced on the activity of monkeys by definitely circumscribed brain lesions were studied by means of a special cage equipped with a recording device for measuring activity. A brief report of these experiments was given at the Second International Neurological Congress in London, in 1935 (Richter and Hines).

METHODS.

A photograph of one of the cages used in these experiments is shown in fig. 1. These cages were 6 ft. long, 6 ft. high and 18 in. wide. The monkey's movements around a central rod which served as an axle were recorded. One end of the rod was connected by gears to two cyclometers on the outside of the cage, and the other end extended freely through a small hole in the opposite side. Every tenth of a revolution of the axle in either direction was recorded. One end of a thin flexible steel rod, 2½ ft. long, was clamped to the axle, the other was connected by a 9-in. length of swivel chain to the collar of the monkey. Thus, the

FIG. 1.—Cage used for measuring activity of monkeys.

animal could reach every corner of the cage, could sit on either of two platforms, one over the central axle, and the other in one corner just above the floor, and still have all of its activity recorded except for a small amount within the range of the chain at the end of the flexible rod. The two cyclometers were read daily.

The room was maintained at a fairly constant temperature, 70° to 80° F., and as free as possible from noise. The animals were fed at 7.30 in the morning just before the cages were cleaned, and again late in the afternoon. The food consisted of bread, carrots, sweet potatoes, cabbage, lettuce and milk.

The brain operations were performed several weeks after the animals were placed in the cages, when it was certain that a constant level of activity had been attained.

In the preliminary experiments the brain tissue was removed by suction through a small glass cannula, while in later experiments the tissue was removed with a cataract knife and preserved for histological study. At the conclusion of the experiments the animals were killed, the brains were removed, fixed in formalin and preserved for macroscopic and microscopic study. Most of the brains were sectioned and stained with Spielmeyer's modification of Weigert's technique; the rest were studied only macroscopically.

Nineteen monkeys used in the experiments were subjected to a total of forty-six operations.

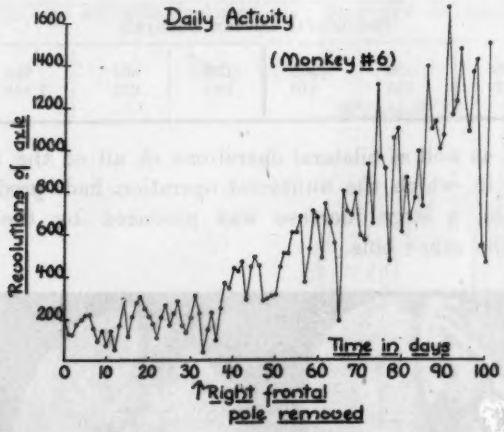

FIG. 2.—Graph showing increase in activity produced by gross removal of the right frontal pole of the brain. Ordinate: Activity in revolutions around axle of cage. Abscissæ: Duration of experiment in days.

RESULTS.

Effect Produced by Gross Removal of Frontal and Occipital Poles.

In the preliminary experiments undertaken for purposes of orientation, a study was made of the effects produced by gross removal of the frontal and occipital poles of the brain.

The record from one of these animals with a unilateral removal of the right frontal pole is shown in fig. 2. It will be seen that the activity increased from a level near 200 revolutions per day to a level near 1,200 and the increase appeared to be permanent.

The frontal poles were removed unilaterally in five animals; in two of these the other frontal pole was removed at a second operation. The results are summarized in Table I. An increase in activity was produced

TABLE I.—GROSS REMOVAL OF FRONTAL POLE.

MONKEY NO.	AVERAGE DAILY ACTIVITY IN FULL REVOLUTIONS OF AXLE						NUMBER OF DAYS OBSERVED AFTER FIRST OPERATION
	10 days before first operation	10 days on plateau after operation	Highest peak after operation	10 days before second operation	10 days on plateau after operation	Highest peak after operation	
6	214	1,142	1,674	—	—	—	88
38	109	295	535	—	—	—	50
57	130	360	545	—	—	—	97
4	68	95	173	95	424	731	67
46	71	224	313	224	397	725	112
PREFRONTAL CORTEX REMOVED.							
49	96	126	205	126	564	824	65
70	57	136	210	136	935	1,453	124

by unilateral as well as bilateral operations in all of the animals. In two animals in which the unilateral operation had produced only a small increase, a large increase was produced by the subsequent removal of the other pole.

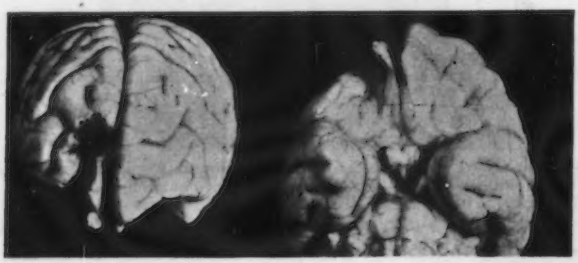

FIG. 3.—Frontal and dorsal views of brain of animal showing unilateral frontal pole lesion which produced marked increase in activity (*see* fig. 2).

The extent of the lesion in the animal whose record was shown in fig. 2 may be seen in the photograph of the frontal and ventral views of the removed brain in fig. 3.

Histological study of the brains of the five animals showed that the lesions were limited to the prefrontal cortical Areas 8, 9, 10, 11 and 12, and to the anterior ends of the caudate and putamen.

Unilateral and bilateral removal of a large area in the occipital region in two animals produced a slight decrease rather than an increase.

Unilateral or bilateral removal of Area 6 alone in two animals also was without effect. Combined removal of Area 6 and the prefrontal cortex in two animals had no effect; it did not produce "marked torpor" or "sluggish motor behaviour" as reported by Fulton, Jacobsen and Kennard (1932).

Effect Produced by Removal of the Entire Prefrontal Cortex Sparing the Striatum.

Further experiments with definitely circumscribed lesions were then undertaken to determine the rôle played (1) by the prefrontal cortex and (2) by the underlying striatum.

Unilateral removal of the prefrontal cortex produced only a slight increase in the two animals operated on; however, subsequent removal

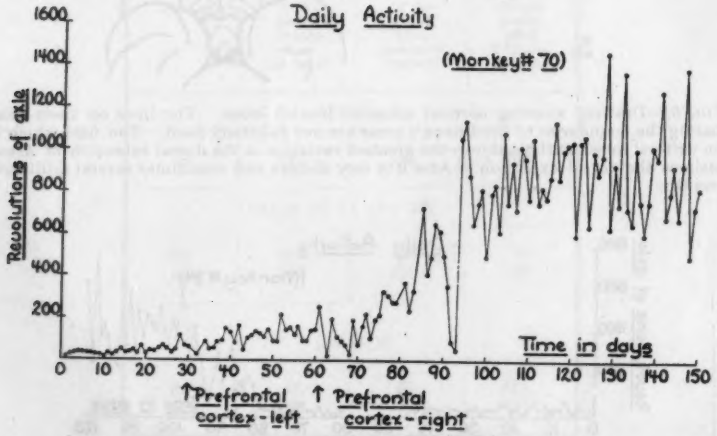

FIG. 4.—Graph showing effect produced on activity by removal of one prefrontal cortex and subsequent removal of the other prefrontal cortex.

of the other prefrontal cortex produced a large increase in activity (*see* Table I). In the record of one of these animals shown in fig. 4, removal of the prefrontal cortex on one side produced an increase from an average level of 57 to 136 revolutions, and removal of the other cortex an increase to an average level of 935 revolutions. The overactivity appeared to be permanent.

The limitation of these lesions to the prefrontal cortex was established by histological studies of the brains and of the extirpated tissue.

It would seem likely then that spontaneous activity is controlled at least in part through the prefrontal cortex, in agreement with the observations made by Jacobsen (1931 and 1936), and Fulton, Jacobsen and Kennard (1932).

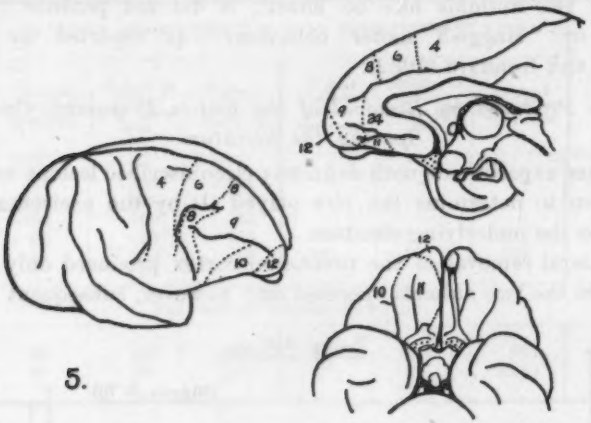

FIG. 5.—Drawing showing cortical areas of frontal lobes. The lines on these charts indicating the boundaries of Brodmann's areas are not definitely fixed. The field which has in the writers' investigations shown the greatest variation is the dorsal extension of Area 8. Sometimes the dorsal extension of Area 8 is very slender and sometimes several millimetres in breadth.

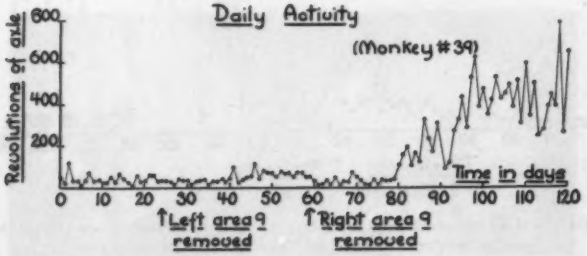

FIG. 6.—Graph showing the effect produced on activity by removal of Area 9 on one side and subsequent removal of Area 9 on the other side.

Effect of Separate Removal of Areas 8, 9 *and* (10, 11 *and* 12).

Having thus shown that activity could be increased by bilateral removal of the entire prefrontal cortex it was decided to determine whether the same large increase could be obtained by bilateral removal of any of the individual parts, as of Areas 8, 9 or (10, 11 and 12) shown in fig. 5.

It was found, in agreement with the results just reported, that unilateral removal of any one of the prefrontal areas produced only a slight, if any, increase in activity. Bilateral removal of Areas 8 or (10, 11 and 12) also had very little effect. Bilateral removal of Area 9 produced a definite increase, as may be seen in the record of one of the animals shown in fig. 6. The average daily activity before operation was 41 revolutions, after unilateral removal of Area 9, 67 revolutions, and after the bilateral removal, 441.

The results of these experiments are summarized in Table II. It

TABLE II.—SEPARATE REMOVAL OF AREAS (8), (9), (10, 11, AND 12).

MONKEY NO.	AVERAGE DAILY ACTIVITY IN FULL REVOLUTIONS OF AXLE		
	10 day period before first operation	10 day period after unilateral removal	10 day period after bilateral removal
(AREA 8)			
66	140	144	102
(AREAS 10, 11 AND 12)			
66	102	97	39
63	110	190	198
(AREA 9)			
39	41	67	441
67	160	121	224

will be seen that in one animal unilateral removal of Area 8 had no effect on activity and bilateral produced a small decrease. Areas (10, 11 and 12) were removed in two animals. Unilateral removal produced a small increase in one; bilateral removal had no effect in one and produced a decrease in the other. The small increase after the unilateral removal in one of the animals can be explained by the fact that the activity was increasing at the time the operation was performed. Unilateral removal of Area 9 produced a small increase in one of two animals and bilateral removal produced a definite increase in both.

Effect Produced by Injuries to the Striatum.

The fact that such a great increase in activity was produced in animals with the gross unilateral removal of the frontal pole involving both the prefrontal cortex and the tip of the striatum, while no increase or only a slight increase was produced by the unilateral removal of the cortex alone, indicated that the striatal injuries must also play an important part.

In order to determine the rôle played by the striatum in the production of overactivity the following experiments were performed. First, an attempt was made to make unilateral lesions in the tip of the

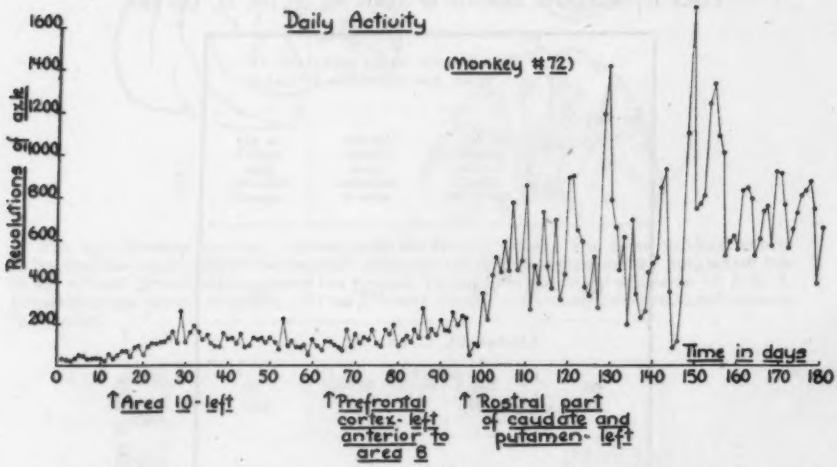

FIG. 7.—Graph showing effect produced on activity by unilateral removal of the tip of the caudate and putamen subsequent to removal of Areas 9, 10 and 11.

striatum without injuring the cortex. These efforts were unsuccessful, due to our inability to localize the lesion and to remove a sufficiently large piece of the striatum. In later experiments the prefrontal cortex was removed unilaterally in one operation. Several weeks later, when it was certain there would be no increase in activity from this operation, the tip of the striatum was removed. It was found that such striatal lesions regularly produced an immediate and great increase. In the record of one of these animals in fig. 7 it will be seen that in contrast to the small increase (from an average level of 38 revolutions to 145 and 145 to 184) produced first by removal of Areas 10 and 11 and then by removal of all of the prefrontal cortex anterior to Area 8, a very great

increase (to 1,057) was produced by subsequent removal of the tip of the striatum (*see* Table III).

Similar records were obtained in two other animals as may be seen in Table III. In monkey No. 69 the small increase from an average level of 199 to 322 revolutions was produced by unilateral removal of left Areas 9 and 10, and a very large increase from an average level of 322 to 828 by subsequent removal of the tip of the caudate and putamen. Removal of Areas 9 and 10 and the tip of the

TABLE III.—INJURIES TO THE STRIATUM.

AVERAGE DAILY ACTIVITY IN FULL REVOLUTIONS OF AXLE.

MONKEY NO. 72		MONKEY NO. 69		MONKEY NO. 71	
10 day period before 1st operation	38	10 day period before 1st operation	199	10 day period before 1st operation	103
10 day period on plateau after removal of Areas 10 and 11 on left	145	10 day period on plateau after removal of Areas 9 and 10 on left	322	10 day period on plateau after removal of left Area 9 and lateral Area 10	229
10 day period on plateau after removal of entire prefrontal cortex on left anterior to Area 8	184	10 day period on plateau after removal of tip of caudate and putamen on left	828	10 day period on plateau after removal of tip of caudate and putamen on left	393
10 day period on plateau after removal of rostral part of left caudate and putamen	1,057	10 day period on plateau after removal of entire prefrontal cortex and tip of caudate on right	929	10 day period on plateau after removal of prefrontal cortex on right	632

striatum on the other side produced an additional increase. Macroscopic and histologic studies made on this brain showed that Areas 9 and 10 and the tip of the striatum had been removed on both sides.

In monkey No. 71 activity increased from an average of 103 revolutions per day before removal of Area 9 and the lateral part of Area 10 to a level of 229. Subsequent removal of the tip of the caudate and putamen produced an increase to 393 revolutions. Removal of the prefrontal cortex on the opposite side produced an increase to 632.

REMARKS.

It was found that in general the increase in activity was much more precipitous in animals with striatal lesions than in animals with lesions limited to the cortex. Thus, in the record (fig. 7) of an animal with a striatal lesion the activity showed an increase three days after operation

and reached a plateau after six days; in the record (fig. 4) of an animal with cortical lesions, activity did not increase until fifteen days after operation, and then only very gradually, not reaching a plateau until thirty-five days later.

Histological Study of Brains.

The degeneration of fibres and nuclei was studied in detail in three animals with cortical and striatal lesions. A short summary is given below.

Monkey No. 72 (lesion of the left prefrontal cortex, head of the caudate and putamen).

The lesion was well circumscribed; it encroached in no way upon Areas 4 or 6, and left in place only the caudal limbs of the infraorbital gyri. The dorsal surfaces of the anterior end of the left caudate and putamen were clearly removed without injury to the globus pallidus. The loss of fibres in the external capsule was great and extended caudally to the level of the middle of the globus pallidus. The loss of fibres in the corpus callosum was confined to its most anterior part, involving little more than the genu. The greatest reduction of fibres in the internal capsule was found medially. Also the number of fibres within the deep layers of the small remnant of the ventral surface of the cortex, i.e. the caudal limbs of the gyri orbitalis and frontalis inferior, was fewer than in similar positions on the normal right side.

The left medial nucleus of the thalamus was definitely smaller than the right and there was perhaps a slight reduction in the lateral nuclear group also. Further, in this brain, where no injury was done to the right side, the reduction of the nerve fibres within and on the ventral border of the lateral division of the left anterior nucleus was particularly clear. There was a definite reduction in the anterior thalamic peduncle, in the fibres which enter the mediodorsal part of the globus pallidus and the medial part of the substantia nigra, and in the stratum sub-callosum.

Although in this brain, as in the others, it was not possible to trace the route taken by the tractus cortico-tegmentalis, nevertheless comparison of the density of fibres both in the thalamus and in the midbrain tegmentum showed clearly a loss on the left medial to the general subthalamic region and lateral to the nucleus ruber, respectively. At the level of the oculomotor nucleus the loss of fibres was obviously confined to the medial part of the basis pedunculi. This loss could be traced into dorsomedial parts of the medial group of descending fibre bundles in the pons, where it gradually disappeared. A search of the midtegmental region caudal to the nucleus ruber revealed what might be considered a scattered loss of fibres dorsal to the main body of the lemniscus systems, and also dorsolateral to the lateral group of tegmental nuclei. In the medulla oblongata at the caudal level of the superior olive, no loss of nerve fibres within the pyramids could be seen, and at this level there was no visible loss of fibres within the tegmentum.

The only fibre degeneration which seemed to be located definitely within the body of the basal ganglia was observed among normal appearing bundles which lie well outside the internal capsule, within the nuclear mass of junction between the caudate and the putamen. These partially degenerated bundles can be followed caudally to the level of the anterior commissure.

The right hemisphere was intact and no disturbance of its blood supply in the region opposite the lesion could be seen.

Monkey No. 69 (*bilateral removal of Area* 9 *and lateral part of Area* 10 *and head of caudate and putamen*).

The diminution of the number of nerve fibres in both the capsula externa and the capsula extrema extended on either side as far caudally as the level of the mid-region of the Island of Reil. There was a reduction of fibres in the subcallosal bundle and in the internal capsule, and in the medial and ventral part of the anterior thalamic peduncle; but within the corpus callosum the reduction was confined to a scattered degeneration within the dorsal part of the genu. The reduction within the internal capsule was circumscribed and confined to the medial division. The more mediodorsal bundles strayed from the internal capsule and at the level of the midthalamic region lay dorsomedially of the corpus subthalamicum and medioventrally of Forel's Field H_2, forming perhaps a tegmental projection system, which, with this technique, could not be traced further than the general subthalamic region. Within the midbrain, the tegmentum dorsolateral to the necleus ruber, a scattered diminution in density of staining appeared.

From the fact that the medial part of the internal capsule swings ventrally to lie on the ventral surface of the midbrain as the pes pedunculi, it followed that the more medially lying concentration of fibre loss was seen in the dorsomedial part of the rostral division of the substantia nigra. This loss involved about the medial one-third of the fibres entering the substantia nigra on the left and not more than the medial one-fourth or one-fifth on the right at homologous levels. At the level of the exit of the root of the third nerve no loss or diminution of nerve bundles could be demonstrated in the substantia nigra. No decrease of fibre content within the globus pallidus was observed.

On the left, the remaining loss in the pes pedunculi was confined to the most medially lying fibres. This loss could be followed into the pontine levels as one in the most dorsomedial bundles. On the right, a very slight loss was seen. Caudal to the mid-pontine region, none could be identified on either side. At the level of the pyramids, the sections of this brain appeared to be normal throughout.

Monkey No. 71 (*removal of all the prefrontal cortex anterior to Area* 8 *and the head of the caudate and putamen on the left side, and of Area* 9 *and the lateral distribution of Area* 10 *on the right*).

The loss in fibre content of both the capsulæ externa and extrema showed a marked gradually decreasing decrement as far caudally as the Island of Reil. A similar gradually decreasing decrement in the number of degenerated

fibres found in the deep white matter of the ventral aspect of the hemisphere was followed from the rostral part of the lesion to the mid-transverse plane of the hemisphere. The loss within the corpus callosum was confined to the region of the genu.

The loss of fibres within the anterior limb of the internal capsule was roughly estimated to be about one-fourth of the total on the right and about nine-tenths on the left. Consequently, the attempt at removal of the head of the caudate was equivalent to cutting both the corticifugal and the corticipetal fibres anterior to the subcortical lesion. Although the actual cortical lesion itself was well confined, the total lesion on the left was practically equivalent to removal of the prefrontal area, anterior to Area 8.

Comparison of degeneration of fibres into the thalamus showed that those on the left were greater in number than those on the right. This loss, visible bilaterally, was followed easily into the ventral part of the lateral group and medial nuclei, and on the left, possibly into the caudal part of the anterior nucleus. There was perhaps a slight decrease in the number of nerve fibres within the lateral nucleus the left side.

In the level of the subthalamus, on the left, many of the degenerated fibres no longer lay within the confines of the internal capsule, but rather in the thalamic tegmentum itself, ventramedially to Forel's Field H_2. Not all of these fibres could be followed rostrally into the midbrain tegmentum (*see* Levin, 1936), and they formed therefore (if this technique is reliable) a projection system into the sub-thalamic tegmentum. Others of these degenerated fibres on the left were followed through many sections, lying lateral to the ganglion interpedunculare. They did not apparently penetrate this nucleus, but gradually disappeared as their destination was sought caudally, forming possibly a projection system into the ventral midbrain tegmentum. Besides this diminution in number of nerve fibres within the ventral part of the midbrain tegmentum there is a scattered loss of stained myelin sheaths within the tegmentum dorsolateral to the anterior reaches of the left nucleus ruber. Further within the dorsal and medial part of the medial division of the globus pallidus there is an apparent decrease in the number of stained myelin sheaths.

In the level of shift of the fibre bundles from a position within the internal capsule to one within the pes pedunculi, the degeneration on the left was confined to the medial fourth, that on the right to a few medially placed bundles. These degenerated fibres left this position in two directions, some shifting dorsally to the medial third of the substantia nigra, others into the medial part of the mediodorsal bundles in the pons.

The subcallosal bundle was greatly degenerated on the left, for on that side it was interrupted in the removal of the rostral caudate-putamen complex. On the right the degeneration of the subcallosal bundle appeared to be as great as on the left as far caudally as the level of the rostral end of the globus pallidus. From this level caudally some normal fibres were found on both the right and on the left.

In summary, the analysis of the fibre degeneration within these brains subjected to removal of the rostral divisions of the caudate or of the putamen did not, with one exception, reveal any projection system not previously recognized by the recent studies of corticifugal systems arising in various portions of the prefrontal cortex (Mettler, 1935; Levin, 1936). This exception was the bundle of degenerating fibres (brain of No. 72) found within the remaining part of the caudate, which could be followed caudally in the ventromedial wall of the telencephalon to be lost in the region ventral to the anterior commissure. That these degenerated fibres actually had their nuclei of origin within the nucleus is doubtful because they could not be identified as degenerated in the brains of Nos. 71 and 69. More likely they were fibres of passage which arose within the medial surface of the frontal lobe.

All three brains have in common great fibre degeneration within the long association systems, such as the capsule externa and extrema, as well as within the subcallosal bundle. In all of these the anterior thalamic peduncle shows great loss of fibres, the greatest in the brains which had suffered the greatest cortical or striatal removals. The greatest diminution in size of thalamic nuclei was found, as should be expected, in the dorsal part of the medial nucleus (Clark and Boggon, 1935; Walker, 1936). The loss of nerve fibres about or within the anterior thalamic nucleus was confined to brains Nos. 71 and 72. (Brain of No. 69 had suffered neither loss of the infra-orbital gyri nor interruption of their inter-regional connections.)

The degeneration of projection systems other than the anterior thalamic peduncle, common to all three of these brains, are those which apparently terminate within the diencephalic tegmentum[1] and the mesencephalic tegmentum, and those which can be traced into the substantia nigra and into the dorsomedial part of the pons. Degeneration of fibres into the globus pallidus was very definite in the brain of monkey 72 from which the prefrontal area had been removed (*see* Mettler, 1935; and Levin, 1936).

That no specific loss of nerve fibres could (with the use of this technique) be allocated to the striatal injuries was disappointing.

[1] Mettler (1935) was able to trace descending degeneration from the prefrontal cortex (judging by the position of the lesion it may have encroached slightly upon Area 6) into the corpus subthalamicum itself and Levin (1936) found no degenerating fibres terminating within the subthalamic tegmentum unless Areas 4 or 6 were included within the area of cortical lesion. One thing is certain, Areas 4 and 6 were not injured in these brains; nevertheless small degenerated groups of nerve fibres were seen within the diencephalic tegmentum, and could be traced no further. Of course, Spielmeyer's technique is not the best method to demonstrate the termination of degenerated fibres. The use of the Marchi technique was out of the question for these brains.

Discussion.

The results of these experiments have brought definite proof of the regulation or control of activity through the frontal poles of the brain, in agreement with the observations made incidentally to other experiments by Lashley (1920), Jacobsen (1931, 1936), and others. They have brought out the fact that the striatum as well as the prefrontal cortex is concerned and that Area 9 of the cortex of Brodmann plays the most important part. This result is not in agreement with the conclusions of Kennard and Ectors (1937). They reported that animals with one hemisphere removed showed " forced " circling movements and deviation of the eyes toward the side of the lesion ; and that removal of Area 8 was solely responsible for the " forced " circling movements inasmuch as removal of the occipital cortex and other prefrontal areas failed to give the same results. These observations led them to conclude that the increased activity which they observed was due to removal of Area 8. The small size of Area 8, as well as the great variation in its extent, add to the difficulties of making lesions which do not include other areas. The simple fact that it is possible to obtain a great increase in activity following an ablation of the prefrontal cortex without including Area 8 (monkey No. 39 showed a very definite increase in activity after bilateral removal of Area 9, completely sparing Area 8 ; and monkeys Nos. 69 and 71 showed increased activity after the striatal lesions were made subsequent to the ablation of Areas 9 and 10, completely sparing Area 8) suggests that the activity described in this paper is a phenomenon quite separate from that described by Kennard and Ectors as " forced " circling movements. The animals under consideration here were seen to circle only when kept in small cages. In larger cages, they were observed to walk back and forth upon the shelves, or to jump up and down from the floor to the sides of the cage. That our one case of bilateral removal of Area 8 (No. 66) did not show " forced " circling may be due to an undetermined slight difference in the operations performed ; for the inclusion or exclusion of an apparently insignificant amount of cortical tissue at certain strategic places makes a great deal of difference in the sequelæ of the operation.

The mechanisms involved in the production of the increase of activity due to prefrontal and striatal lesions are not known. Viewed from a behaviour level the increased activity might be due to a change in the animal's disposition manifested in an increased desire to escape. We were unable to detect changes of such a nature. An increased hunger or thirst, if present and unsatisfied, might produce the increased

activity. Our animals did not show a noticeable increase in appetite or thirst (no measurements were made). Furthermore, they were never without food or water. Still another possibility is that we are dealing with a perseveration tendency; in other words, that once started running about the cage the animal is unable to stop. However, we could not discover the manifestations of any other perseveration tendencies. For example, the animals did not continue to make chewing movements after the food was swallowed. Viewed from a more strictly physiological angle the increased activity may be regarded as a result of a release phenomenon, that is, the removal of the inhibitory influences from the higher centres may permit external stimuli to pass on freely without hindrance or inhibition to lower reflex centres. Actually the animals did show a greatly heightened distractability, responding to all kinds of stimuli.

In spite of the increase in our understanding of the nerve-fibre relations between the prefrontal cortex and subcortical centres, the exact nervous mechanisms which are involved in the production of an increase in spontaneous activity are unknown. The cortical and striatal ablations described in this paper interrupt simultaneously the corticifugal and the corticipetal connections alike. Further, there is no way to distinguish between the results of interruption of projection systems which discharge into the sensory nuclei of the thalamus from those which discharge into the motor nuclei of the general brain-stem (globus pallidus, the substantia nigra, the pons nuclei and the tegmentum of the subthalamus, midbrain and medulla oblongata).

The fact that the increase in activity was usually delayed after cortical lesions but appeared almost immediately after striatal lesions is difficult to explain. It occurred to us that the greater delay in the increase resulting from cortical lesions as compared with the striatal lesions might be due to the fact that the cortical lesions were bilateral and produced a greater shock due to the greater amount of extirpated cortical tissue. However, a strikingly sharp increase was shown in an animal after bilateral removal of prefrontal cortex and of the tip of the striatum. In this animal the removal of the prefrontal cortex of both sides did not prevent the appearance of a sudden increase in activity.

The fact that the same operation produced unequal increases in activity in different animals, and also that unilateral lesions produced a larger increase than bilateral lesions in some animals, may possibly be explained in terms of the greater variation of a phylogenetically newer system. Of course, the condition of the animals, as well as the

animals' adjustment to the cage and the surroundings, may play an important part in modifying the results.

Summary.

(1) Permanent overactivity was produced in five macaques by gross unilateral or bilateral removal of the frontal poles of the brain.

(2) These lesions included the prefrontal cortex and the tip of the caudate and putamen.

(3) Unilateral removal of the prefrontal cortex in two animals produced only a slight increase in activity. Subsequent removal of the other prefrontal cortex produced a great increase.

(4) Unilateral and bilateral removal of Areas 8, or of 10, 11 and 12 in two animals, had little or no effect on activity.

(5) Bilateral removal of Area 9 produced a definite increase in activity in two animals.

(6) Overactivity was definitely produced in three animals by removal of the tip of the caudate and putamen after the previous removal of the prefrontal cortex on the same side had failed to produce an increase.

(7) It was concluded that activity is definitely controlled through the prefrontal cortex, particularly Area 9, and also through the striatum.

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SPONTANEOUS HÆMATOMYELIA: A SHORT REVIEW AND A REPORT OF CASES ILLUSTRATING INTRAMEDULLARY ANGIOMA AND SYPHILIS OF THE SPINAL CORD AS POSSIBLE CAUSES.[1]

BY J. CLIFFORD RICHARDSON.

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(1) INTRODUCTION.

Hæmorrhage holds one of the leading positions amongst the causes of disease in the nervous system. Hæmorrhage into the spinal cord is decidedly rare, in contrast with the frequent occurrence of cerebral hæmorrhage. This has been explained by the fact that the spinal arteries are long, narrow and tortuous, being subjected to less severe pressures than the cerebral vessels (Williamson, 1911). The clinical picture of intraspinal hæmorrhage, spinal apoplexy, was first described as an entity comparable to cerebral hæmorrhage early in the nineteenth century. The term "hématomyélie" was introduced by Ollivier d'Angers (1827).

The usual conception of hæmatomyelia is that of a large intramedullary spinal hæmorrhage with a tendency to spread longitudinally over several segments. It has been further designated as "tubular" and as "annular" hæmatomyelia. The hæmorrhage shows a marked predilection for the grey matter, a fact that seems adequately explained by the looser texture and greater vascularity of the grey substance as compared with the white. The posterior horns are invaded more often than the anterior horns. Experimental proof of a tendency to spread in grey matter mechanically has been provided by the experiments of Goldscheider and Flatau (1897) and of Lépine (1900), in which fluids were injected under pressure into spinal cords.

The causes of hæmatomyelia are multiple. Most authors state that

[1] From the National Hospital, Queen Square, London.

trauma is much the commonest of these. A second large group is that termed "spontaneous hæmatomyelia," which includes these cases of primary hæmorrhage without trauma. Hæmatomyelia has been described as occurring secondarily in syringomyelia, intramedullary spinal tumours, syphilitic myelitis, hæmorrhagic diatheses, arteriosclerosis, miliary aneurysm of the spinal arteries (Hebold, 1885), and in acute myelitis. Smaller hæmorrhages of no clinical significance may occur in some of the above conditions, in acute anterior poliomyelitis, and in general acute infections and intoxications. The classification followed by Gowers (1886), and by Doerr (1906-7) in his comprehensive review is: (1) Traumatic. (2) Spontaneous. (3) Secondary (tumour, syringomyelia, &c.). (4) Accessory (small hæmorrhages not giving rise to any clinical symptoms). This last group should probably not be included under the term "hæmatomyelia" with its customary, though arbitrary, meaning of a large central hæmorrhage.

Arteriosclerosis and hypertension, which are of such prime importance in cerebral hæmorrhage, have been shown to play little or no part in the ætiology of hæmatomyelia. The age incidence of the latter is earlier than that of cerebral hæmorrhage, being commonest in the twenties. Men are much more commonly affected than women. In Doerr's review of thirty cases with autopsies, there were twenty men and ten women.

Age in Years ..	0-10	11-20	21-30	31-40	41-50	51-60	61-70
No. of Cases ..	1	6	11	5	1	2	4

This report is particularly concerned with the "spontaneous" type of hæmatomyelia. On account of the great rarity of the condition, and of the uncertainty of data in many previous writings, the subject is one of many conflicting views. Gowers commented on the need for an accumulation of more exact observations, and the need still remains. More detailed considerations of ætiology will be discussed after the case reports.

(2) Case Reports.

Descriptions of four cases of hæmatomyelia follow, three with post-mortem findings, and one clinical report of a non-fatal case.

Case 1.—*Hæmatomyelia caused by an angioma. A young man, aged* 25, *who was a patient in the National Hospital, under the care of Dr. Hinds Howell, from November* 19, 1936, *until his death on December* 13, 1936.

Clinical History.—He was well until October 1, seven weeks before coming to hospital. At that time he noticed a gradual onset of numbness in the toes and in the ball of his right foot. There was a tingling sensation whenever he

put his foot to the ground. During the first week the numbness gradually spread upwards to involve the whole foot; then in another fortnight the back of the right leg and the inner surface of that knee also felt numb. One week after the onset of symptoms he began to have a constant dull ache across his back in the lumbar region, which was aggravated particularly by bending his head forwards. In the fourth week he began to have an intermittent slight weakness of his right leg. On October 31 he found while playing football that he could not run or kick as well as usual. The next day his legs and back were stiff and painful. On November 2nd the pain in his back and legs increased and kept him awake all that night. In the afternoon he vomited several times and there was a rapidly progressive weakness of his legs so that by evening he could not stand. On November 4 the legs were completely powerless and anæsthetic. The pain had then disappeared from his legs but remained severe in his back. He had complete retention of urine and fæces. From that time, that is for two weeks before coming to hospital, he remained in the same condition.

His past health had been good. Two weeks before the onset of his illness he had an infected scratch on his left forearm, which discharged pus in small amounts for several weeks. He also developed a large pustule on the left index finger three weeks before admission.

Clinical examination.—He was a tall muscular young man, whose legs were paralysed, and who was obviously in great pain. The cranial nerves were normal except for a fine nystagmus on full lateral deviation of the eyes. He was unable to sit up, and on trying to do so there was a deviation of the umbilicus upwards and to the left. The legs were flaccid and completely powerless. The tendon reflexes were normal in the arms, absent in the legs. There was no response to plantar stimulation. The right upper abdominal reflex was feeble, the right lower absent; those on the left were both normal. All forms of sensation were absent below the 12th thoracic segmental level on the right and the 1st lumbar level on the left. A higher band of moderately impaired sensation to pin-prick and heat and cold was present between the 5th and 9th thoracic levels on the right, with a band of hyperalgesia between it and the region of complete loss (fig. 1). There was a fairly pronounced tenderness over the lower lumbar vertebral spines. Both knee joints were swollen and contained fluid.

The temperature at first was normal except for occasional rises to as high as 100° F. There was no leucocytosis or anæmia (R.B.C. 5,200,000 per cu. mm.; Hb. 95 per cent.: W.B.C. 7,600 per c.mm.). The urine contained many pus cells. The cerebrospinal fluid was clear, colourless and under normal pressure, with no signs of block on jugular compression. Cells were not increased in number. Total protein was raised to 0·09 per cent., and the Pandy test was weakly positive. The Lange gold curve was 0000110000. The Wassermann reaction was negative in the cerebrospinal fluid and blood.

Summary.—A young man who had gradual onset of numbness and later weakness of his right leg for four weeks, then sudden severe pain in the legs

and back, followed by complete paralysis of legs, bladder and bowel. Examination suggested a complete transverse lesion of the cord at about the first lumbar segment, with a higher intramedullary lesion from 5th to 9th thoracic segmental levels.

A provisional clinical diagnosis of acute myelitis was made, but as he had at the time of onset of his symptoms a purulent infected wound of his left forearm, and later developed a large pustule on the left index finger, the possibility of a staphylococcal abscess in the epidural space could not be ruled out. An exploratory laminectomy was therefore performed, with a negative result.

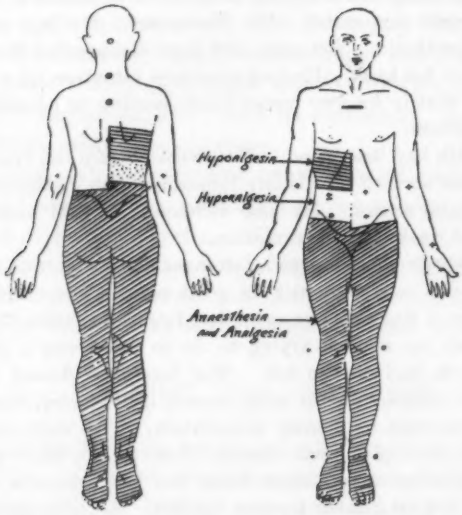

FIG. 1.—*Case* 1. Chart of sensation showing the upper band of impaired sensation to pin-prick, heat and cold on the right side from Th.5 to Th.9, and complete loss of all forms of sensation below a level of Th.12 right, and L.1 left. Tendon reflexes are indicated.

He became progressively worse owing to an intractable infection of the urinary tract. He developed high fever and a mild toxic jaundice before his death on December 13.

Post-mortem examination.—Autopsy showed the cause of death to be an acute suppurative pyelonephritis with a gangrenous cystitis.

On the surface the spinal cord looked normal except for slight diffuse swelling in the lumbar enlargement. On sections the cord showed a rounded, tubular cavity containing blood-clot, running down from the lower part of the 4th dorsal segment to the lower end of the cord. Above, the cavity was small, and situated in the right posterior horn. Lower, at the junction of the 9th and 10th thoracic segments it became more median, lying at the apex of the

posterior columns just behind the posterior commissure. In the 12th thoracic segment the hæmorrhage was much larger and passed across the mid-line in the grey commissure. It became largest, nearly 1 cm. in diameter, at the lower border of the 1st lumbar segment, and below this ran down as a central cavity in the posterior columns to the lower end of the cord (fig. 2).

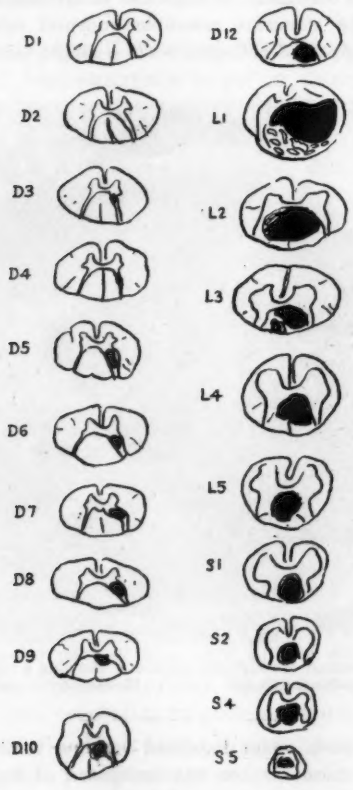

FIG. 2.—*Case* 1. A drawing of sections of the spinal cord at various levels, showing the position of the hæmatomyelia. A central column of blood is present from Th.3 to S.5 segments. The angioma is indicated in the 1st lumbar segment. Above, the hæmorrhage is in the right posterior horns; below, it is in the posterior columns.

The physical signs coincided accurately with this distribution of the hæmorrhage. The band of sensory loss from 5th to 9th thoracic segmental levels was due to hæmorrhage in the right posterior horn. From the 9th to the 12th thoracic levels the hæmorrhage had spread out of the grey matter, and in those dermatomes sensation was preserved. At the 1st lumbar segment

the massive hæmorrhage had caused a complete transverse lesion, below which motor power, sensation and reflex activity were lost.

Histological examination.—On the posterior part of the section through the area of largest hæmorrhage one could faintly distinguish macroscopically a small, oval, yellowish, porous-looking area of abnormal tissue. Microscopically, this was found to be a small angioma confined to that segment (fig. 3). It consisted of a localised collection of large and small thin-walled blood sinuses. In a few of these the structure resembled normal veins, but they mostly consisted of a thin layer of collagen, with a single lining layer of flattened

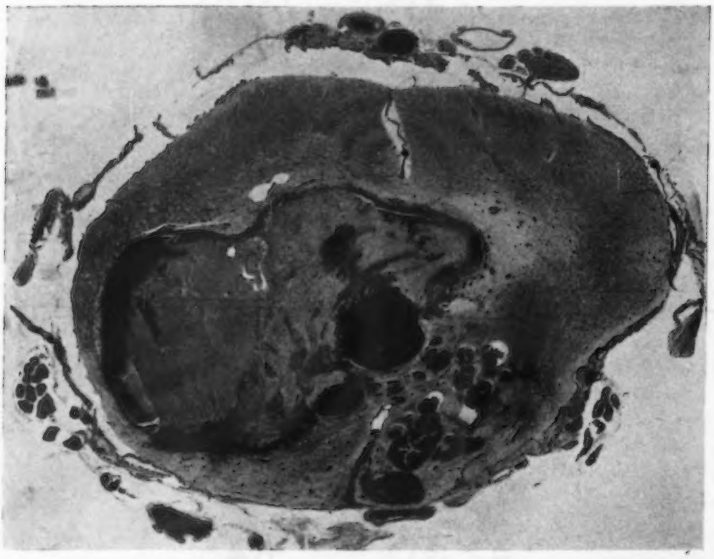

FIG. 3.—*Case* 1. Section through the angioma, showing a ruptured vessel and the adjoining large hæmorrhage. (× 6.) Hæmatoxylin and Van Gieson.

epithelium. There were some localized hyaline thickenings of the walls. The tissue between these sinuses was composed of hyperplastic glial tissue infiltrated by hæmorrhage, of scattered bands of connective tissue and some nerve fibres. An actual point of rupture of one of the larger sinuses could be seen in some of the sections.

The clinical symptoms suggest that a slow leakage occurred at first, then a more massive hæmorrhage. This severe hæmorrhage following a game of football was probably provoked by the spinal venous congestion ensuing upon the strenuous exertion. Trauma was in that sense a secondary precipitating factor.

The hæmorrhage appeared recent, being composed of intact red blood-cells

centrally, with a relatively small amount of blood pigment at the periphery. This pigment was greatest in amount in the 1st and 2nd sacral segments. The white matter at the margin of the hæmorrhage was severely degenerated and there was some proliferation of capillaries, and perivascular infiltration of lymphocytes. In the grey matter of both anterior and posterior horns there were pronounced degenerative changes in the nerve-cells, with well-defined neuronophagia and falling out of cells (Plate I, fig. 4).

Vascular tumours and malformations of the spinal cord are rare, but in the cases reported hæmatomyelia is not an uncommon complication. Lissowsky (1933) reports a case in a 49-year-old man, very similar to the above described, in which there had been no symptoms prior to the terminal hæmatomyelia. The vascular lesion was very similar to ours, and was almost invisible macroscopically. Also in Buckley's case (1936) of a large cervical angioma there was little or no clinical manifestation until a hæmorrhage in the grey matter extending to the lower thoracic region terminated fatally. In that angioma a more mature type of blood-vessel is described. Similar vascular lesions reported by Guillain, Schmite and Bertrand (1932), by Ohlmacher and by Bremmer and Rossolimo (quoted by Lissowsky) have very similar features and were complicated by hæmatomyelia. Russell (1932) reported a case of capillary hæmangioma of the spinal cord with extensive cavitation, which may have been the relic of a hæmatomyelia. Such "angiomata" are probably developmental vascular malformations rather than true tumours. They tend to occur in either the cervical or lumbar enlargements.

True vascular tumour, or hæmangioblastoma, may also occur in the spinal cord, though much less commonly than its favourite site in the cerebellum. (Lindau, 1930-31; Bucy, 1932). They are said to be situated in the posterior part of the cord almost exclusively (Wolf and Wilens, 1934). They may or may not be associated with the features of Lindau's disease (viz. cerebellar tumour, angioma of retina, and cysts of pancreas and kidney). Their true neoplastic nature is shown histologically by endothelial proliferation, excessive formation of reticulin fibres, and the absence of nerve fibres between the smaller vascular channels. The association of hæmatomyelia with these tumours is not as well defined as in the angiomatous malformations above described. Spinal hæmangioblastoma is often associated with cystic cavitation of the cord or with syringomyelia, which may possibly in some cases be the end result of a hæmatomyelia, as suggested by Russell. Clinically they are said to give rise to frequent exacerbations of symptoms. Detailed considerations of the pathological features of the various types

of vascular maldevelopments and tumours is beyond the scope of this report. The distinction between neoplasm and maldevelopment in these lesions is somewhat difficult, and there is a good deal to suggest that hæmangioblastoma also begins as a vascular anomaly.

Case 2.—A man, aged 58, who was admitted to the National Hospital under the care of the late Dr. Kinnier Wilson on September 12, 1936, and died on January 1, 1937.

Clinical history.—He was well until April, 1935, seventeen months before coming to hospital. At that time he was suddenly awakened at night by severe pain across the lower abdomen. There was a rapidly increasing weakness of the legs in the next two days. Twenty-four hours after the onset he had developed a numb patch over the upper part of the front of his right thigh. After two days the legs, bladder and bowel were completely paralysed and he had a numb dead feeling up to the waist. In St. Mary's Hospital soon after the onset an examination of the cerebrospinal fluid showed a strongly positive Wassermann reaction, 15 lymphocytes per c.mm., a raised globulin content and a meningitic gold curve. The blood Wassermann was also positive and he was treated by administration of iodide, mercury and bismuth.

He remained in the same state for the first month and then gradually recovered. Bladder and bowel functions returned to normal in the second month. Power returned more slowly in the legs and he suffered a constant, tight, painful sensation in the legs and about the hips, with painful flexor spasms of the legs. He was able to walk with crutches five months after the onset. One year after the onset of symptoms he began to have much more severe pain in the legs and this brought him to hospital.

Clinical examination.—He looked old, thin, weak, and tortured by continued pain. The pupils reacted a little sluggishly to light, otherwise the cranial nerves were normal. The arms and trunk were normal. There was a severe spastic paraplegia, the right leg somewhat more rigid and weak than the left. There was some local wasting of the glutei, hamstrings and quadriceps. No definite sensory level could be determined on repeated careful examination. Appreciation of light touch was slightly impaired over both feet and legs below the knees. The sense of position and passive movement was grossly impaired in the right foot and decreased on the left. Vibration sense was lost in both legs. The knee and ankle jerks were exaggerated with a right ankle clonus and bilateral extensor plantar responses.

Examination of the other systems was negative except for fairly pronounced arteriosclerosis in the retina and peripheral vessels.

The cerebrospinal fluid was now normal and the Wassermann reaction was negative in the cerebrospinal fluid and blood.

Summary.—This was a 58-year-old syphilitic male who, seventeen months previously, had a sudden onset of severe abdominal pain and complete paralysis of legs, bladder and bowel. He recovered progressively for several months but marked weakness and rigidity of the legs remained. One year after the

onset he began to have more severe pain in the legs. There was no sensory level but the muscular wasting suggested a lesion as high as the 2nd lumbar segment, and the early history suggested a lesion as high as the 10th or 11th thoracic segments.

Dr. Wilson's clinical diagnosis was syphilitic "thrombomyelia," an apt term of his own invention designating thrombotic softening of the spinal cord.

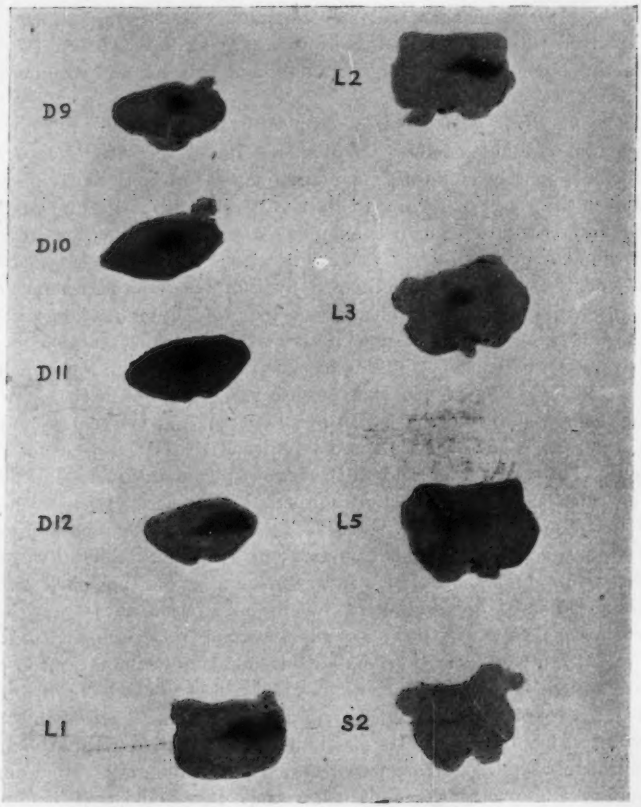

FIG. 5.—*Case* 2. Sections of the spinal cord in thoracic and lumbar segments, stained for iron to show the position of the old hæmorrhage. (× 2·3.)

In hospital the patient became progressively worse from an intervening infection of the bladder and bowel which led to his death twenty months after the onset of symptoms.

Post-mortem examination.—Examination of the spinal cord showed slight thickening and sticky adhesions of the leptomeninges over the dorsal surface. Some softening could be felt in the region of the 12th thoracic segment.

Sections of the cord showed the brown scar of an old hæmatomyelia extending from the 9th thoracic to the 4th lumbar segments. The pigmented area stained deeply by the Prussian blue reaction for iron (fig. 5). Above, the area of old hæmorrhage was small and rounded, lying just behind the posterior commissure. It became larger as it was traced downwards and showed a lateral extension to the right and lateral margin of the cord in the 12th thoracic and 1st and 2nd lumbar segments, thus involving the posterior column, base of posterior horn, and lateral column. At the 1st lumbar segment it also involved the base of the anterior horn. In the 3rd and 4th lumbar segments the hæmorrhage was again small and tubular, and confined to the right posterior column.

Histological Examination.—Microscopically, there was no cavity, nor were there any free red blood-cells. There was a heavy deposit of old brownish blood-pigment, mostly contained in macrophages forming thick cuffs around the vessels in the posterior columns (Plate I, fig. 6). Several lymphocytes were scattered amongst the pigment-laden phagocytes. In some areas the vessels were surrounded by a pure round-cell infiltration. In other places the whole thickness of the vessel was infiltrated by lymphocytes, sometimes causing a slight inward bulging of the intima. A localized inflammatory reaction of this type was well defined in one large pial vein. This reaction, occurring distinct from the perivascular cuffing by macrophages containing iron pigment, was the most definite evidence of syphilitic vascular disease that was found. The exact source of hæmorrhage was not detected, but it seems possible that rupture occurred in one of these small syphilitic (?) vessels.

A dense glial scar was present in the area of pigmentation, most pronounced centrally, with a lateral projection through the posterior horn to the lateral column in some areas. Large astrocytes with heavy neuroglial fibres were seen by phosphotungstic acid hæmatoxylin staining. There was also a pronounced marginal gliosis, with tufts spreading into a thickened pia.

Pronounced local destruction of myelin and nerve fibres was shown by Loyez stain as pale areas in the area of pigmentation and scarring (Plate I, fig. 7). There was also a well-defined ascending degeneration in the posterior columns and descending degeneration in the pyramidal tracts (Plate I, fig. 8).

This long, tubular and flattened strip of blood pigment is probably the relic of an extensive hæmorrhage. Its distribution is similar to that of the first case, though probably the hæmorrhage was smaller. The history of rapid onset with pain supports clinically the contention that the lesion was hæmorrhagic. The hæmorrhage cavity had been entirely filled by a glial scar, and the resulting picture was one of old hæmorrhage rather than of softening.

There have been a few reports of syphilis as a cause of hæmatomyelia, though it would seem distinctly uncommon. In the case report of Roger, Antonin and Poinso (1928), entitled "Syphilitic Softening of the Cord," the pathological findings were very similar to the case here reported.

R. T. Williamson (1911) recorded another case of syphilitic hæmatomyelia. Chung (1926) reports thirty-four cases of syphilitic paraplegia of rapid onset. Though thrombosis was probably the cause in most of these cases, some may well have been due to hæmorrhagic lesions. Chevallier and Desoille (1930) consider hereditary syphilitic vascular lesions as the most important cause of vascular weakness in spontaneous hæmatomyelia, though their report contains no convincing proof of that opinion. In Brooks' report (1916) of four cases of hæmatomyelia, two were syphilitic.

Case 3.—Spontaneous Cervical Hæmatomyelia.

This was a 31-year-old man seen in consultation at a L.C.C. Hospital by Dr. Purdon Martin. I am grateful to him for the following clinical notes.

Clinical history.—The patient was well until three weeks before his death.

His illness began suddenly with severe pain in his neck radiating to both shoulder blades. Severe pain persisted and the following day he gradually lost the use of his left arm. Micturition was difficult from the onset, passing to complete retention just before his admission to hospital on the twelfth day of the condition. His left leg had been a little weak for a few days before coming into hospital.

Clinical examination.—The left pupil was slightly constricted, otherwise the cranial nerves were normal. There was a flaccid paralysis of the left arm with absent reflexes. Power was good in the right arm, but all tendon reflexes were sluggish. Power was moderately impaired throughout the left leg, with slight rigidity, increased knee and ankle jerks, and an extensor plantar response. In the right leg power was normal, knee and ankle jerks normal, and plantar response doubtfully extensor. Sensation to pin-prick and cotton-wool was impaired over the 6th and 7th cervical dermatomes on the left. There was a moderate impairment of sensation to pin-prick over the whole right side of the body below the 4th cervical distribution. The cerebrospinal fluid was normal; the protein estimation was 0·025 per cent.; there was no evidence of block; and the Wassermann reaction was negative in the cerebrospinal fluid and blood.

The signs thus clearly indicated an intramedullary lesion of the cervical enlargement extending up to the 4th cervical segment, and producing a Brown-Séquard syndrome. The diagnosis was considered to rest between some form of acute myelitis and a vascular lesion, probably the former.

Full notes of his progress are not available. He remained acutely ill and on October 1 became unconscious. On that day he passed a blood clot from the bladder. There was thought to be a slight right facial weakness. He died later on the same day three weeks after the onset of symptoms.

Post-mortem examination.—Nothing grossly abnormal was detected in other organs than the brain and spinal cord. The brain was generally con-

gested but showed no petechial hæmorrhages or other focal macroscopic lesions. Examination of the spinal cord at autopsy showed an irregularly rounded hæmorrhage into the left side of the cord from the 3rd to the 7th cervical segments. The hæmorrhage was mostly in the grey matter involving both anterior and posterior horns. Above, it extended also into the left lateral column.

A portion of the cervical spinal cord was received for examination at the National Hospital pathological laboratory. The cord had been severely damaged in removal, so that the naked-eye picture could not be satisfactorily studied in the fixed material, and only part of the mid-cervical cord was sufficiently intact for section cutting. In the sections made from the 6th cervical segment there was a well-defined transversely-lying oval area of hæmorrhage in the left lateral column (fig. 9). The anterior and posterior

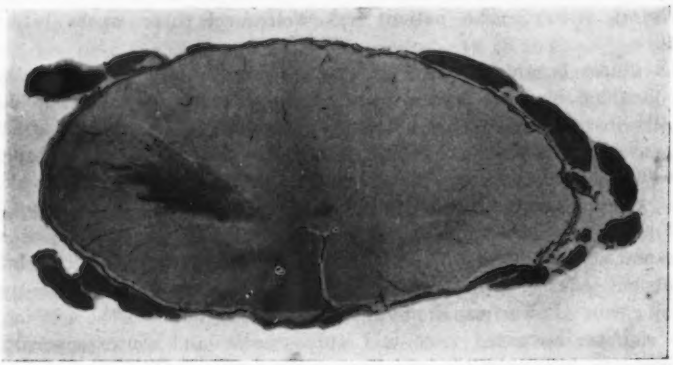

FIG. 9.—*Case* 3. Recent hæmorrhage in the left posterior horn and lateral column (× 5.) Hæmatoxylin and Van Gieson.

horn cells on that side showed moderately severe degenerative changes, namely, central chromatolysis with poorly staining eccentric nuclei. The neighbouring blood-vessels in the cord were congested, but no vascular disease or anomaly was demonstrable. There was no evidence of any acute inflammatory process.

The investigation in this case was necessarily incomplete. It serves merely to illustrate the clinical features of hæmatomyelia, with a rough picture of the pathology. Though no vascular weakness was demonstrated, it is quite possible that a source and a cause of the hæmorrhage were missed.

Case 4.—*Cervical hæmatomyelia. Survival with residual weakness.*

A man, aged 38, *who was in the National Hospital under the care of Dr. Hinds Howell.*

Clinical history.—This patient, a painter, was well until September 18, 1935. On that morning, while at work, he felt a sudden pain in both arms

from shoulder to finger tips, which continued, and was followed six hours later by a noticeable weakness and clumsiness of his fingers. In the subsequent few hours the weakness in his hands increased to almost total paralysis. On awakening the next morning his hands and fingers were powerless, and he was unable to move his right leg; the pain had then entirely disappeared. Power seemed good in his elbows, shoulders and in his left leg. He was too weak to sit up in bed. His hands at this time felt numbed and senseless. There was a numb, cold sensation over the right foot and leg up to the lower thigh, which spread up over the right thigh and the right half of the abdomen in the following hour. Also, on the second day, he had complete retention of urine, though he could feel his bladder distended.

He was taken to Fulham Hospital on the third day of his illness. There, the bladder function gradually recovered, but his condition remained otherwise unchanged for two or three weeks.

About three weeks after the onset, power began to return in the right leg and the left arm. They improved rapidly for a fortnight and then more gradually up to the time of coming to hospital. The numb sensation of the right leg and lower trunk passed off entirely in the first few weeks. The right hand showed no recovery for three or four months, and remained much weaker than the left. Wasting was noticed in his hands a few months after the onset.

About four months after the beginning of his trouble he noticed, when taking a hot bath, that he could not appreciate heat with his left leg. This sensory disturbance remained unaltered from that time.

Clinical examination.—The cranial nerves were normal except for a slight left ptosis. Motor functions were normal in the neck and shoulder girdle.

Arms: There was wasting along the front of the right forearm, particularly on the ulnar side, and marked wasting of all the small muscles of the right hand. On the left there was wasting of the first dorsal interosseous muscle only. There was marked weakness in flexion of the right fingers and wrist, power being fairly good in extension. There was no weakness of movements at the shoulder and elbow. Power was good in the left upper limb except for slight weakness in flexion and adduction of the thumb. There was no inco-ordination or fibrillation of the arm muscles, and rapidly alternating movements were performed well.

Trunk: Movement of the right side of the chest was considerably diminished, and the intercostal muscles below the third were felt to be powerless. There was some weakness of the right abdominal muscles, and the umbilicus deviated to the left.

Legs: There was no wasting of the leg musculature. Slight rigidity was noted throughout the right; the tone was normal in the left leg. Flexion of the right hip and dorsiflexion of the right foot were weak; other movements were of normal power, with no weakness on the left.

Sensation: There was a moderate hypoalgesia to pin-prick over the trunk on both sides from the 2nd to the 10th thoracic segments, and over the ulnar

border of the right arm. Appreciation of heat sensation was slightly impaired over the left lower abdomen and over the outer part of the left leg.

Reflexes	*Right*	*Left*
Biceps-jerk	Normal	Weak
Triceps-jerk	Normal	Weak
Supinator-jerk	Normal	Weak
Finger-jerk	Absent	Weak
Abdominal	Weak	Normal
Knee-jerk	Brisk	Normal
Ankle-jerk	Normal	Weak
Plantar reactions	Extensor	Flexor
Ankle clonus	None	None

His gait was marked by dragging of the right foot.

Summary.—A 38-year-old man who experienced a sudden onset of pain in the arms and then weakness of the hands. This was followed the next day by total paralysis of the hands, right leg and bladder, weakness of the trunk muscles, and subjective sensory loss over the right leg and right side of the trunk. Recovery occurred gradually with residual weakness and wasting of the upper limbs and a spastic weakness of the right leg. Loss of heat sensation was noticed in the left leg some time after the onset.

Examination fourteen months after the onset showed weakness and wasting of the flexor muscles of the right hand and wrist and of the mucles of the left thumb, with weakness of the right intercostal and abdominal muscles. The right leg was slightly rigid and weak. Sensation to pin-prick was impaired from the 2nd to the 12th thoracic segmental areas bilaterally and heat appreciation was diminished over the left leg and lower abdomen (Th. 10 and 11 and L.5).

Diagnosis.—The lesion in this case can be accurately localised as an elongated, central lesion in the cord, involving the anterior horns in the lower end of the cervical enlargement, spreading down in the posterior commissure and posterior columns, causing a dissociated sensory loss over both sides of the trunk and loss of deep sensation in the legs. It apparently extended out into the right lateral column at some point to cause the ipsilateral pyramidal tract signs and the partial contralateral sensory loss due to encroachment on the spinothalamic tract.

The involvement is so well localized to the central part of the cord as to make a diagnosis of myelitis unlikely. The picture is rather like that of syringomyelia. The sudden onset in a previously healthy man makes one fairly confident of a diagnosis of haematomyelia with persistent cavitation and gliosis of the cord.

It seems reasonable that some local vascular weakness was present, probably in the cervical enlargement, to account for this apparently spontaneous hæmorrhage. In the absence of signs of arteriosclerosis and of syphilis or other infection, an intramedullary tumour, or vascular maldevelopment, such as in Case 1, are possibilities.

(ε Discussion.

(i) *Symptomatology.*

The onset of spontaneous hæmatomyelia is characteristically sudden, as these cases all illustrate. In Case 1 the prodromal symptoms of spreading numbness and then weakness of one leg, preceded the rapid onset of a complete paraplegia. In Case 2 and 4 the symptoms reached their maximum only after twenty-four and forty-eight hours. Many reported cases have had a much more rapid onset, a complete powerlessness of the legs supervening within a few hours or even minutes. In fact Gowers and others doubted the possibility of prodromal symptoms in primary hæmatomyelia, and suspected that all such cases were myelitic in origin.

Though symptoms vary with the site of the lesion, there is usually a total paraplegia of the legs, a definite sensory level below which all forms of sensation are lost, and paralysis of the bladder and bowel.

Pain is said to be common but not invariable. It was a symptom common to all four of the cases here reported, and was a striking feature in the first two cases. The pain is probably of central origin due to hæmorrhage into the posterior horns. It seems unlikely that swelling of the cord, sufficient to compress the nerve roots, would occur. In all cases the initial pain in the affected limbs disappeared with the arrival of complete paralysis. In Case 1 there was also severe pain in the back which persisted throughout the illness. In the syphilitic case the occurrence of severe pain in the legs, a year after the onset, suggests a relation to the forming of a glial scar in the posterior horns. In Case 4 the minimal occurrence of pain corresponds with the suggested location of the hæmorrhage, in that it did not apparently affect the posterior horns to any great extent.

Tenderness over the vertebral spines, as was noted in one of these four cases, has been frequently described in the older writings on hæmatomyelia.

The *prognosis* in primary hæmatomyelia is difficult in view of the several different possibilities for the course of the disease. In severe cases death may occur in a few hours or days, and Doerr mentions two cases of sudden death. The rapidly fatal cases are chiefly those of hæmorrhage into the cervical cord. In other cases a fatal outcome may result after a few days or weeks, in which the course is almost always secondary infection of the urinary tract, or decubitus. The three fatal cases here reported fall into this group, though in the

second case a terminal infection occurred as a much later event. Though exact figures are not available, it appears that a large proportion of the cases are less severe and do not terminate fatally. It is in some measure characteristic of hæmatomyelia that the symptoms, after reaching a maximum, often with an initial picture of spinal shock, subside to a considerable degree. Gradual recovery occurs over a period of several months as in our fourth case, leaving permanent more or less severe paralyses and sensory loss.

It is conceivable that a long, central hæmorrhage in the spinal cord may eventually result in a pathological and clinical picture very like syringomyelia. Minor suggested from such observations the "hæmatomyelogenous" theory of development of syringomyelia. Krause and Glatt (1934) and others have reported clinical observations corroborating the conception of central cavitation of the cord beginning as a hæmorrhage. D. S. Russell's report of angioma with cavitation and gliosis is a case in point. The fourth case here reported also had a final clinical picture not unlike syringomyelia. Though central cavitation and gliosis may undoubtedly be produced, the picture of true syringomyelia or syringobulbia has its own distinct features and has not been reproduced by old hæmorrhage.

In this discussion of the symptoms and course of the diseases, the articles and reviews of Gowers, Oppenheim, Batten, Lépine, Minor and Doerr have been consulted. The reader is referred to those works for more detailed descriptions of clinical features, differential diagnosis and treatment.

(ii) *Ætiology.*

As previously mentioned, it is generally stated in the literature that trauma is much the commonest cause of hæmatomyelia, but if one considers this in the usual sense of a large, central hæmorrhage spreading longitudinally, it seems probable that the importance of this factor has been exaggerated. Some of the early case reports have been merely clinical without post-mortem confirmation. In other cases of direct injury to the cord, a localized pulping, softening and hæmorrhage has been termed hæmatomyelia (Ballance, 1897; Thorburn, 1889). The diagnosis of hæmatomyelia is often based on clinical findings suggestive of spinal cord damage over several segments, the assumption being that a central hæmorrhage has occurred.

Holmes (1915), in his study of spinal injuries of warfare, was impressed by the fact that hæmorrhages were by no means the outstanding pathological feature of direct injury to the spinal cord. A true

hæmatomyelia, defined as above, was not found in any of his fifteen cases. "Hæmorrhages, generally small, but occasionally of considerable size, are usually found in these softened areas" (at the site of injury), "but they are more common and as a rule larger in grey, than in white matter. In many cases, however, hæmorrhages have been few or very small and they are evidently not a feature of the condition." The distant lesions which he found over several segments on each side of the local pulping of the cord, and which seemed of much more significance than hæmorrhage, were œdema and softening, localized swelling of axones, degeneration of nerve-cells, patches of necrosis and vacuolation, and peculiar cylindrical non-hæmorrhagic cavities. Similarly in contusion and concussion, hæmorrhages were minute and scattered, and the striking features were œdema, softening, focal necrosis, and vacuolation of white matter.

Jefferson (1936), more recently, has expressed the same opinion, minimizing the importance of hæmatomyelia in spinal cord injuries. He states that though local hæmorrhage is present at the site of a direct injury to the cord, it is not a feature of those cases of fatal contusion of the cervical cord in which the only gross lesion is a diffuse swelling. To quote from his article concerning spinal contusion: "It is doubtful whether such a state as 'hæmatomyelia' actually exists. It is more probable that the clinical syndrome which we call, and no doubt shall continue to call, 'hæmatomyelia,' is due to a local neural disruption, to relatively bloodless contusion, rather than to intramedullary clot."

Granted that hæmorrhage may occur over several segments in a few cases of spinal cord injury, and may well be most marked in the gray matter, it is then usually associated with marked softening, and is a hæmorrhagic softening, rather than a pure, central blood-clot.

The high incidence of traumatic hæmatomyelia in the literature if further increased by terming "traumatic," cases in which the precipitating factor of a hæmatomyelia was excessive exertion or mild direct injury (Zwirn, 1928; Fox, 1876; Sharkey, 1891). Oppenheim (1911) remarked on the difficulty in judging the importance of trauma in such cases, and Doerr pointed out that there was probably some underlying weakness of spinal blood-vessels. It seems likely that most of such cases belong in the group "spontaneous hæmatomyelia." Thus, in our first case in which there was an intramedullary angioma, the actual hæmorrhage was precipitated by the exertion of playing a game of football.

The term, "spontaneous hæmatomyelia," is best understood as

meaning a primary, non-traumatic, elongated, central hæmorrhage of the cord, occurring in the absence of preceding symptoms of a spinal cord lesion. It is difficult to conceive such a hæmorrhage occurring from healthy vessels, and the writer takes the view previously emphasized by H. Brooks (1916), that there is always some fault in the vessels. (In the latter's four cases the hæmorrhages were ascribed to syphilis and arteriosclerosis with an added factor of alcoholism.) In this sense such hæmorrhages are really secondary, but the term "secondary hæmatomyelia" would be better reserved for those cases occurring with spinal cord tumour, syringomyelia and myelitis, which had in themselves previously produced spinal symptoms. Thus, in the first two cases here reported, the term spontaneous hæmatomyelia is applicable. Though the hæmorrhage was caused by a minute angioma, and by syphilitic vascular disease, the hæmorrhage was the first clinical manifestation of spinal disease.

A useful analogy can be drawn with the intracranial condition of spontaneous subarachnoid hæmorrhage. In that syndrome there is always some vascular disease and we now recognise "berry" aneurysms of the circle of Willis to be much the commonest form of this. In the much rarer condition of spontaneous hæmatomyelia, observations are too few and incomplete for any comparable certainty of our knowledge of ætiology. Intramedullary vascular tumours and malformations may eventually prove the commonest causes, with syphilis, acute myelitis and arteriosclerosis contributing a smaller share.

(iii) *Summary.*

Four cases of the rare condition "spontaneous hæmatomyelia" have been presented. The first and second of these exemplify two of the causes of the condition.

In the first case there was a small angioma in the 1st lumbar segment of the spinal cord which had ruptured, causing a central hæmorrhage from the 4th thoracic to the lowest sacral segment. The "angioma" was considered a developmental vascular lesion rather than a tumour. Previously reported cases having a similar cause have been cited.

The second case was one of old hæmatomyelia occurring with syphilitic meningomyelitis. A central hæmorrhage has occurred from the 9th thoracic to the 5th lumbar segment, leaving an elongated strip of gliosis containing a large amount of old blood pigment.

The third case was one of cervical hæmatomyelia in which the exact

cause was not demonstrable, since pathological examination was incomplete. In the fourth case hæmatomyelia was not fatal, but left permanent sensory and motor changes resembling those of syringomyelia.

The clinical features and causes of spontaneous hæmatomyelia have been reviewed with reference to these cases.

Traumatic hæmatomyelia has assumed a false position of importance in the incidence of true hæmatomyelia. Hæmorrhage is often overstressed in the conception of the pathology of spinal cord injuries.

Spontaneous hæmatomyelia should be considered as primary, non-traumatic hæmatomyelia, and is probably always due to disease or maldevelopment of the spinal vessels. Vascular maldevelopments, similar to that found in Case 1, comprise one of the commonest known causes of the condition.

These cases were studied clinically and pathologically at the National Hospital, Queen Square, during the tenure of a resident staff appointment. I am very grateful to Dr. J. G. Greenfield for the photomicrographs and for his great assistance in the pathological examinations. My thanks are also due to the above-mentioned Honorary Physicians for permission to publish the cases.

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LEGENDS FOR PLATE

FIG. 4.—*Case* 1. Anterior horn cells in the eleventh dorsal segment showing degenerative changes caused by the neighbouring hæmatomyelia. Neuronophagia is well marked. (× 400.) Nissl stain.

FIG. 6.—*Case* 2. Masses of old blood pigment forming cuffs around the vessels in the posterior columns. (× 100.) Prussian blue reaction.

FIG. 7.—*Case* 2. Twelfth dorsal segment. Pale area of myelin destruction in the region of old hæmorrhage, involving the right posterior column, posterior horn and lateral column. The meninges are somewhat thickened. (× 7·6.) Loyez stain.

FIG. 8.—*Case* 2. Second lumbar segment. Local myelin destruction and descending pyramidal tract degeneration. (× 7·6.) Loyez stain.

PLATE I.

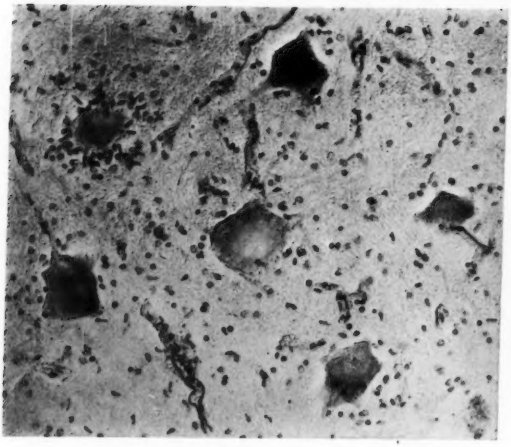

FIG. 4.

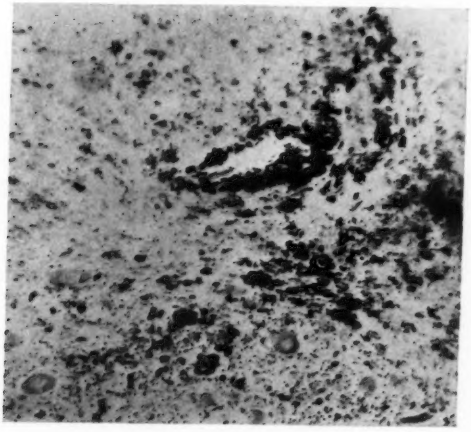

FIG. 6.

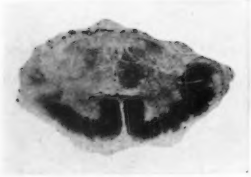

FIG. 7.

FIG. 8.

To illustrate article by J. Clifford Richardson.

ON NORMAL DISCS IN PATIENTS WITH CHIASMAL LESIONS.[1]

BY ADAMS A. McCONNELL AND ALAN J. MOONEY.

In the majority of cases of pituitary tumour the optic discs are pale, but in a certain number of cases the discs are normal in appearance or "within normal limits."

When the existence of a tumour in the neighbourhood of the chiasma has been finally established and the early case notes are reviewed in retrospect, doubt has sometimes been cast on the observation that the discs were normal in appearance. There is a widespread notion that in patients with the gross field defects that are found in such cases the discs must have been atrophic in appearance and some surgeons have been inclined to question the accuracy of the ophthalmologist's observation. This series of case reports is an attempt to show that his considered judgment may be a valuable element in diagnosis.

The paper is based on six cases of tumour involving the chiasma in which the discs were normal.

Case 1.—*K. F., male, aged* 38. *Headache, vomiting and defective vision. Bitemporal hemianopsia. Discs normal. Gross enlargement of pituitary fossa. Operation, retrochiasmal pituitary adenoma. Death. Post-mortem examination.*

The patient was admitted to the Richmond Hospital, Dublin, under the care of Dr. H. Lee Parker, on May 22, 1936.

About Christmas, 1935, his vision became blurred, printed words being indistinct and "all mixed up." Some time later objects also became indistinct.

In March, 1936, he began to suffer from headaches of a dull aching type with acute exacerbations. The acute pain was felt usually in the frontal and occipital regions, but occasionally "seemed to come out through my ears."

In April, 1936, vomiting started. It was provoked particularly by any sudden movement and occurred frequently.

Examination.—General medical and neurological examinations were negative. Ophthalmological examination showed: Right eye, corneal nebula. Vision corrected $\frac{6}{12}$, J 2. Left eye, small foreign body in the cornea. Slight hypermetropia. Vision corrected $\frac{6}{24}$, J 3. Fundi normal. Ocular movements and pupillary reactions normal. Visual fields showed complete bitemporal

[1] From the Neurological Department of the Richmond Hospital, Dublin.

hemianopsia with sparing of the macula in the right eye. Basal metabolic rate −24. Glucose tolerance curve normal. Wassermann reaction negative. Radiographic examination by T. G. Hardman revealed an extremely large sella turcica with almost complete destruction of the dorsum sellae.

June 27, 1936: Transfrontal exposure of chiasmal region. The right optic nerve passed straight backwards from the optic foramen. It appeared normal. At first sight the pituitary fossa appeared empty, but when the nerve was traced backwards a tumour appeared in the middle line below the chiasma. A needle was passed into it and some old blood was aspirated. An incision opened a firm-walled cavity containing a considerable amount of dark blood. With a curette and with pituitary rongeur forceps, a small amount of tissue which seemed to line the wall of the cavity was removed and part of the wall was excised. The condition seemed to be that of a hæmorrhagic cyst in a

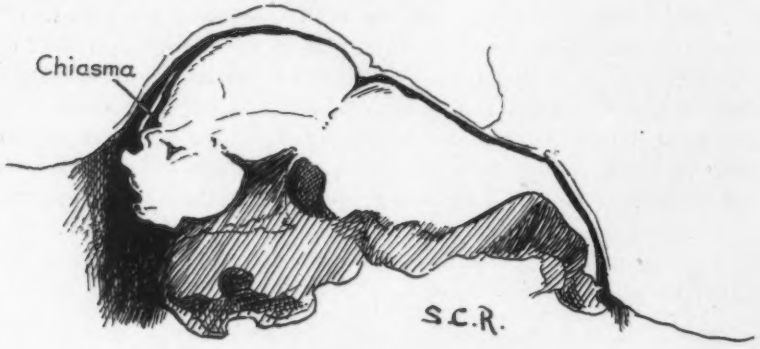

FIG. 1.

pituitary tumour and it was hoped that the evacuation of the cyst would be sufficient to relieve the patient's symptoms. The wound was closed. The patient seemed to be recovering satisfactorily, but forty-eight hours after the operation he became comatose and died.

Post-mortem examination revealed a large pituitary tumour filling most of the 3rd ventricle and extending backwards to the pons. The optic chiasma was reduced to a thin membrane as it stretched across the front of the tumour (fig. 1). Below the chiasma were the remnants of the cyst which had been evacuated at the operation. Even when distended with blood it did not seem probable that the cystic portion would have pressed on the optic nerves. The optic nerves seemed to emerge abruptly from the anterior surface of the flattened chiasma; they were not flattened. On the upper aspect of each nerve at its junction with the chiasma was a deep groove caused by the anterior cerebral artery.

Microscopic diagnosis: chromophobe adenoma.

Case 2.—D. O., male, aged 40 years. Headache and vomiting for five months. Nearly blind. Discs normal. Pituitary insufficiency. Operation, retrochiasmal tumour. Recovery of vision. Left homonymous hemianopsia.

The patient was referred to the Richmond Hospital, Dublin, on July 12, 1937, by Mr. Deane, of Belfast, on account of blindness.

About the middle of March, 1937, he noticed that "words ran into each other," and later that his vision was "misty." Occasionally he had diplopia.

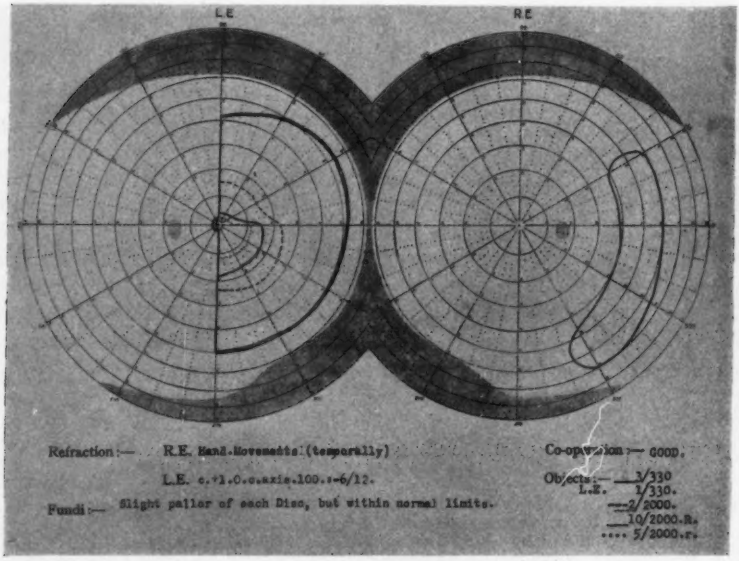

FIG. 2.

A diagnosis of nicotine poisoning was made, but appropriate treatment for that condition had no effect.

In April he began to suffer from headaches, which were very severe at their onset. He had one attack of vomiting after a meal and frequent attacks of nausea.

He had been putting on weight for the past two years and "had not to shave as often as formerly."

Examination.—Fat, flabby and pale in appearance. The chin looked as if he had never shaved and was sparsely furnished with hair. He was intelligent and co-operative. No abnormal neurological findings.

July 14, ophthalmological examination. Right eye, no perception of light, pupil inactive. Left eye, perception of light in nasal field and pupil reacts to

stimulation of temporal side of retina. Discs normal, arteries small, veins slightly congested.

The floor of the sella turcica and the dorsum sellæ were eroded.

July 18, ventriculography showed that the outline of the 3rd ventricle was transverse rather than vertical, and this suggested the presence of a large tumour encroaching on the ventricle from below.

Operation, right transfrontal exposure of the chiasmal region.

The dura was opened and the anterior part of the falx resected. The

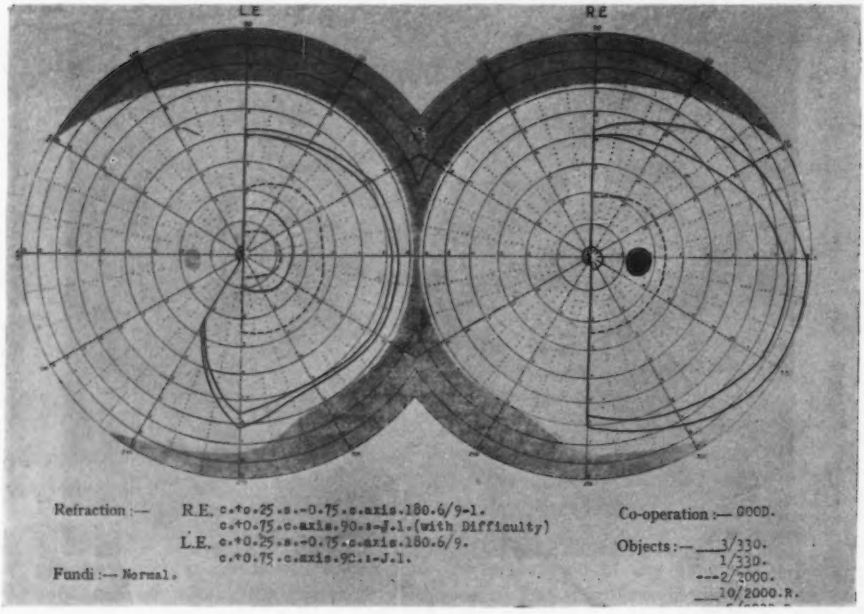

FIG. 3.

mesial aspects of the frontal lobes were adherent behind the free edge of the falx. Elevation of the right frontal lobe exposed the right optic nerve, which was normal in its appearance and course. The chiasma was exposed, apparently pushed forward by the tumour which appeared below and somewhat in front of it. A needle was passed into the growth and some yellowish fluid withdrawn. It was not oily. An incision allowed a large quantity of this cystic fluid to escape, and the cyst wall collapsed. A portion of the wall was removed and the wound closed.

The patient was very irritable and disoriented for several days after the operation, but on the sixth day he became rational and said that he could see. On the tenth day he was reading the newspaper comfortably.

Perimetry on August 8, 1937, showed a left homonymous hemianopsia (fig. 2), and further improvement was shown in the charts made on September 15 and November 7 (fig. 3).

Microscopic finding: Chromophobe adenoma.

Case 3.—*H. D., male, aged* 34. *Spontaneous subarachnoid hæmorrhage. Headache and failing vision. Bilateral central scotoma. Normal discs. Operation, subchiasmal aneurysm opened and packed with muscle. Complete relief of headache and disappearance of scotomata.*

The patient was admitted to the Richmond Hospital, Dublin, August 11, 1936.

History.—The patient had been in perfect health until May 16, 1936. On that day at 7.30 p.m. he was brushing his clothes when he cried out suddenly and fell to the ground unconscious. He vomited several times before the ambulance arrived. On admission to the Meath Hospital at 8.55 p.m. he was unconscious. The right side of the body was in a state of flaccid paralysis and the left in a state of spasm. He was grinding his teeth and had bitten his tongue. The pupils reacted to light. About an hour after admission he became very restless and his left arm and leg had to be held forcibly. He was incontinent of fæces. A quarter grain of morphia made him quiet and he slept. There was a small lacerated wound over the right eye. Next day the right hemiplegia was less marked and he rapidly regained power in his limbs. For two days he was extremely restless except when under the influence of morphia. He talked incoherently and vomited everything that was given to him.

May 19 he was quieter and apparently more conscious of his surroundings. Vomiting continued.

May 20: Dr. H. Lee Parker saw him and made the following note: "No clear evidence of illness prior to recent episode. At present complaining of headache; is somewhat drowsy and stupid and remembers nothing prior to Saturday, May 16, at 2 p.m. He converses rationally and has no speech defect. Examination shows suggestive œdema of both optic discs, but it is not definite. Weakness right side of face and slowness in the movements of the right arm and leg. Tendon reflexes more active on *left* side. Plantar response flexor both sides. Neck rigid. Kernig positive."

He suggested the possibility of rupture of a congenital aneurysm of the circle of Willis and recommended lumbar puncture. The cerebrospinal fluid contained much blood. The Wassermann reaction was negative.

From this date the patient made a rapid recovery except for the persistence of a dull wandering headache. He left hospital apparently well on June 25, 1936.

On July 22 he got a sensation as of something spinning in his head, and he fell. He could hear, but could not move his limbs. The attack lasted but a few minutes. After this attack the headache returned, and became so severe that he was admitted to the Richmond Hospital on August 11, 1936.

Examination.—Blood-pressure systolic 95 mm., Hg. diastolic, 60. There were no neurological signs or symptoms with the exception of nystagmus on extreme lateral deviation of the eyes. The optic discs were normal and the visual fields full. R.V. corrected, $\frac{6}{18}$. L.V. corrected, $\frac{6}{12}$. The defective vision recorded was probably due to the fairly high refractive error, the patient not having worn glasses previous to his admission to hospital. The cerebro-spinal fluid showed no increase in the number of cells or in the amount of protein. Pressure 120 mm. of water. Radiographic examination of the skull

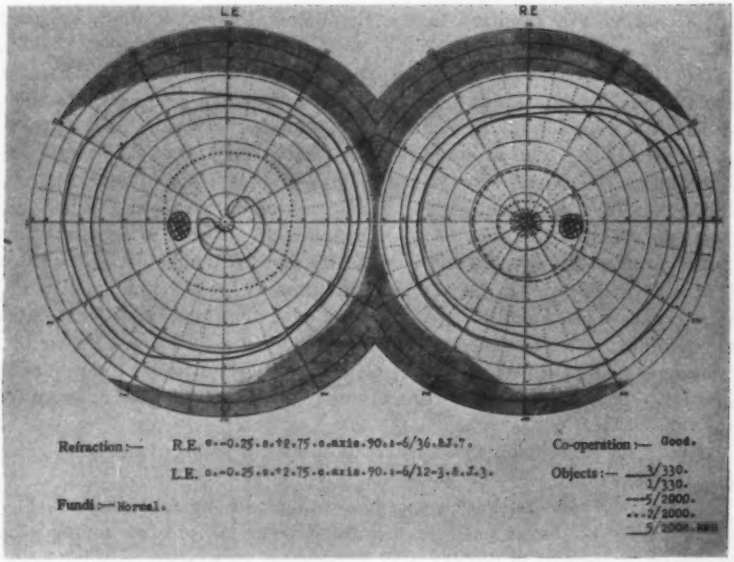

FIG. 4.

showed no abnormality, while that of the chest revealed considerable fibrosis but no active pulmonary disease.

September 25: Encephalography. Nothing abnormal was disclosed. Exacerbation of headache. Headache continued and became worse until October 30, when the patient complained of blurring of vision.

November 1: Vision, right eye $\frac{6}{36}$; left eye $\frac{6}{12}$. Perimetry revealed a central scotoma in each eye (fig. 4). That in the left for red objects only.

The flaccid paralysis of the right side of the body immediately after the initial attack of subarachnoid hæmorrhage suggested a sudden anæmia of the left side of the brain probably due to rupture of an aneurysm of the left common carotid artery. There was no satisfactory explanation of the bilateral central scotoma. Bitemporal defects, both scotomatous and non-scotomatous, have been described in cases of aneurysm of the circle of Willis, but we found

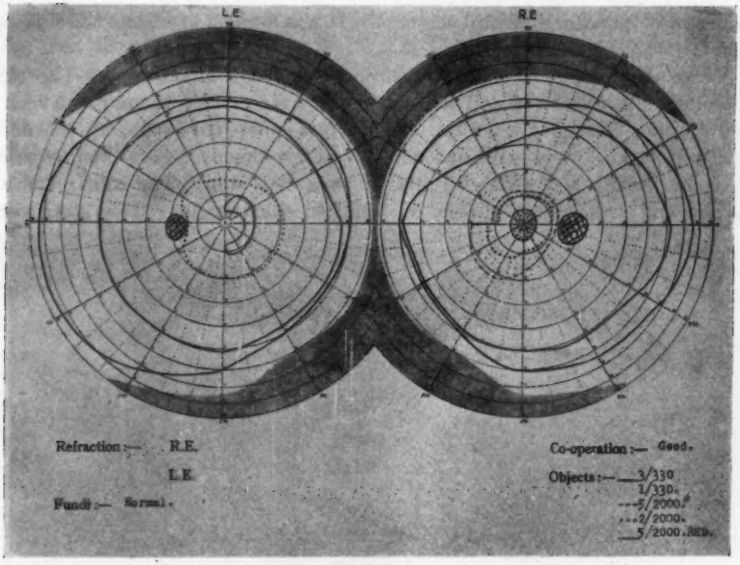
L.E
R.E
Refraction :— R.E.
L.E.
Fundi :— Normal.
Co-operation :— Good.
Objects :— 1/330
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FIG. 5

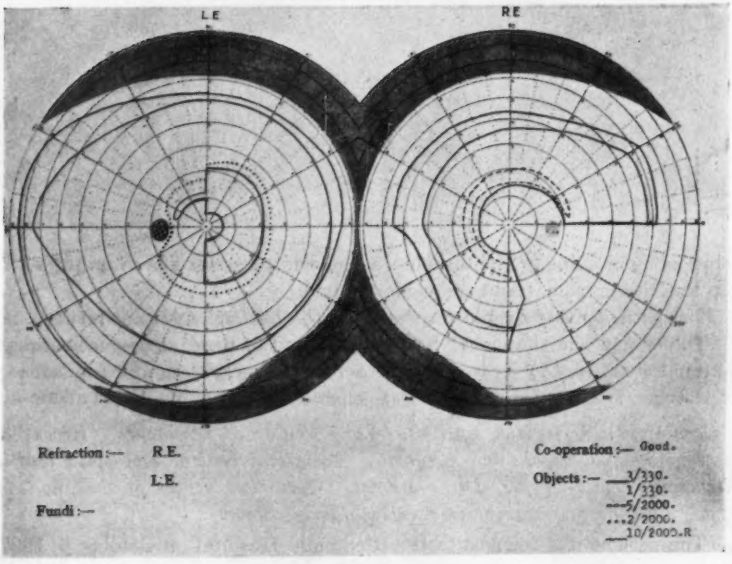
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FIG. 6.

no record of a bilateral central scotoma. It was decided to explore the chiasmal region.

November 9, 1936: Right transfrontal exposure of chiasma. The right optic nerve was straight and normal in appearance. No tumour was seen in the pituitary fossa, but when the chiasma was exposed, a dark rounded tumour appeared just below it. When touched with the forceps it gave the impression of being elastic and tense. Pulsation was not seen. The aneurysm was opened and muscle immediately pushed into the opening. This stopped the

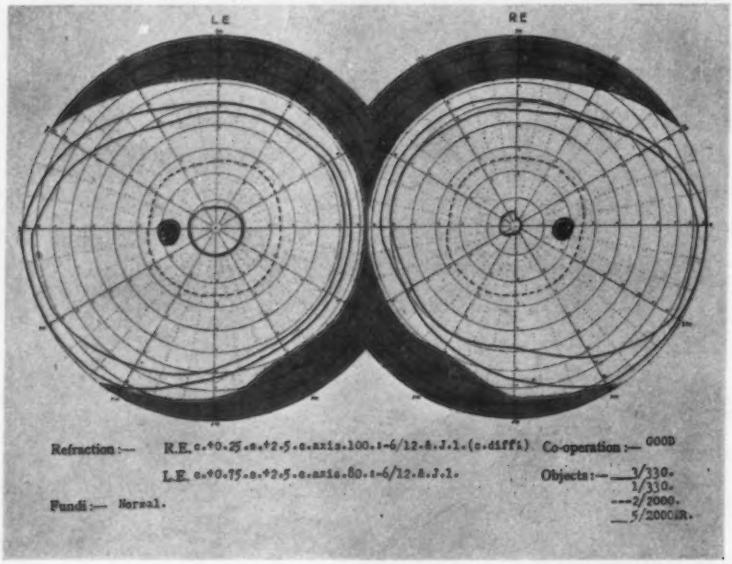

FIG. 7.

voluminous bleeding. The muscle was held in place for fifteen minutes. The flap was then replaced and the wound closed.

The patient made a rapid recovery and the headache did not return.

The changes in the visual fields (figs. 5 and 6) were at first alarming, but the final chart (fig. 7) showed complete recovery of vision, and the last report on October 7, 1937, indicates perfect general and visual health.

Case 4.—D. S., female, aged 49. Long history of headaches. Recent onset of vomiting, polydipsia and polyuria. Bilateral central scotomata and later bitemporal hemianopsia. Discs normal. Operation, nerves normal, no tumour seen. Post-mortem examination, retrochiasmal tumour.

The patient was referred to the Richmond Hospital on October 6, 1937, as a pituitary tumour by Dr. R. H. Micks, to whom we are indebted for the following notes.

Previous history.—At the age of 18 she had pleurisy and at 20 she had what was described as exophthalmic goitre. About ten years ago headaches started and have continued. They were described as "pressure on the head."

June, 1936, she began to suffer from excessive thirst and the passage of large amounts of urine, "That was the first thing." At the same time she had bronchitis.

July, 1936, she stated that she was treated in a London hospital for goitre

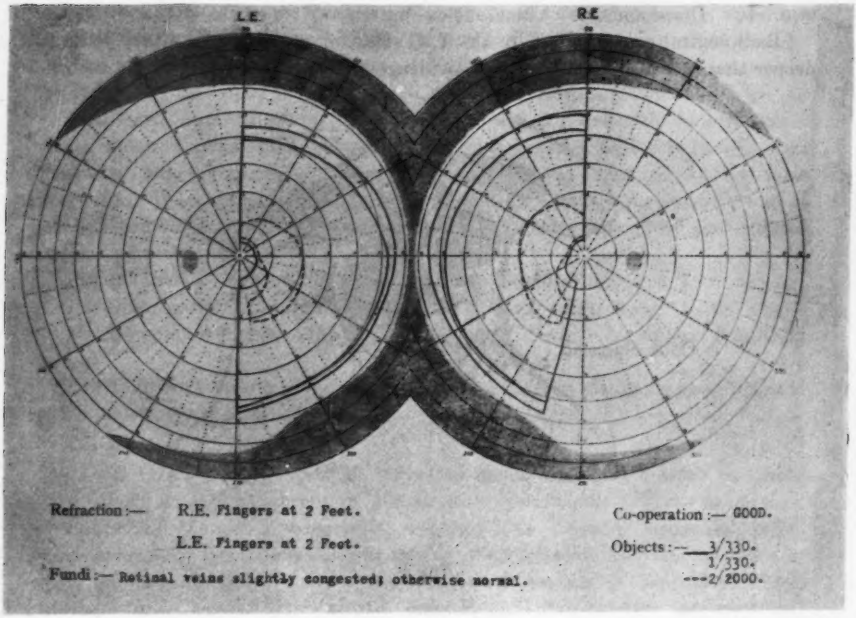

FIG. 8.

and was given thyroid extract. Vomiting began at this time and made the headache worse.

March, 1937, she noticed that the vision of the right side of the right eye was blurred and about a week later that of the left side of the left eye was similarly affected. She occasionally had double vision.

April, 1937, her eyes were examined by Dr. L. Werner who reported: Right eye vision, corrected, $\frac{6}{18}$ centro-cæcal scotoma for colour. Left eye vision, corrected, $\frac{6}{9}$, centro-cæcal scotoma for colour and relative scotoma for white. Fundi normal, peripheral fields full. Because of the history of early impairment of lateral vision special attention was devoted to the peripheral fields, but no defect was discovered in them. Wassermann reaction negative.

Weight 9 st. 8 lb. May, 1937, headache very bad; vomiting. September, 1937, bitemporal hemianopsia and central scotomata.

On admission to the Richmond Hospital the patient appeared dull and apathetic and complained of severe headache. The thyroid gland was not enlarged. General neurological examination was negative. Basal metabolic rate was −1. Average fluid intake 170 oz.; output 130 oz. Blood-pressure 120/85.

Ophthalmological examination.—R.V. fingers at two feet. L.V. fingers at two feet. Discs normal. Visual fields (fig. 8).

Radiological examination by Dr. T. G. Hardman. "The pituitary fossa is deeper than normal but there is no evidence of erosion of its floor or absorp-

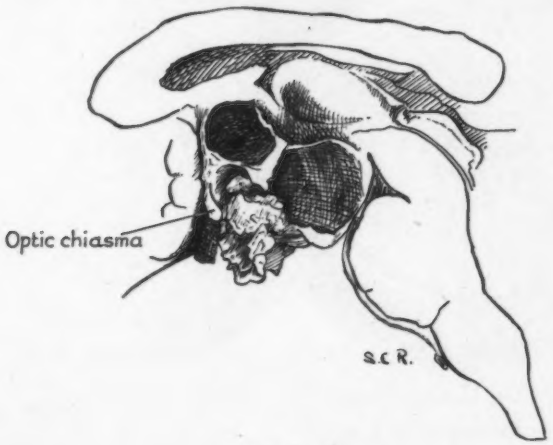

FIG. 9.

tion of the clinoid processes. Cranial bones are very thick, particularly in the frontal region in which the appearance is almost suggestive of a hyperostosis. No other abnormality shown."

October 14, 1937: Operation. Avertin and local anæsthesia. The usual frontal flap for transfrontal exposure of the chiasmal region was made. The bone was over one centimetre thick and had a very irregular inner surface. Passage of the dural separator for the medial section of the bone was difficult and produced excessive bleeding, so that when the bone-flap was turned back the blood-pressure had fallen from 120/80 to 85/55. A saline and glucose intravenous infusion was given and the patient reacted well, but it was considered wiser to postpone the rest of the operation. All bleeding was controlled and the wound closed.

The day after this operation the patient still showed signs of shock. The temperature was subnormal and the thirst and polyuria worse, and she had

great difficulty in getting up thick sputum. Within four days she had improved except for a bronchitis which precluded any possibility of a general anæsthetic.

October 18, 1937. Second operation. Local anæsthesia. The bone flap was turned down and the usual exposure of the chiasmal region made. The chiasma was somewhat but not markedly prefixed and the optic nerves short and normal in appearance and course. There was no sign of tumour, nor could one be felt on exploration of the pituitary fossa. As the patient had been very restless all through the operation it was not thought right to split the chiasma and proceed farther, moreover it was thought that a transventricular approach through the foramen of Munro might be better. The wound was then closed.

The pulmonary condition became rapidly worse after this operation and on the third day developed into definite pneumonia. She died two days later.

Post-mortem examination.—The floor of the 3rd ventricle bulged downwards, widening the interval between the optic tracts and displacing the chiasma forwards. The remnant of the pituitary gland was attached to the tuber cinereum. When the optic nerves were drawn downwards the anterior wall of the 3rd ventricle appeared to bulge also and it was embraced by the anterior cerebral arteries.

Fig. 9 shows a drawing of the region in mesial section.

The optic nerves appeared to be normal in every respect.

Microscopic diagnosis: craniopharyngioma. The pituitary gland itself was normal.

The following case may be cited in this connection although the chiasmal region was not inspected during life.

Case 5.—D. J., male, aged 29. Failing vision and photophobia for three years, along with development of acromegalic appearance. Severe headaches. Normal discs. Left homonymous hemianopsia. Greatly expanded sella. Trans-sphenoidal operation. Slight relief. Four months later two attempts to expose growth by transfrontal operation failed because of general pressure. Fatality three weeks after second operation. Post-mortem examination, retrochiasmal tumour of the pituitary gland.

The patient was admitted to the Richmond Hospital, Dublin, on June 26, 1929. Referred by Dr. Greene of Galway as a case of pituitary tumour.

History.—Normal childhood and adolescence. Towards end of 1924 his right eye was struck by a gun trigger. There was some conjunctival hæmorrhage, but the eye was not injured. Libido had been absent for eight years.

In 1925 he began to complain of headaches starting over the right eye and radiating along the right side to the occiput.

In 1926 he noticed he could see more clearly with the right eye closed. About the same time he began to suffer from photophobia. Change in facial appearance began. One attack of epistaxis.

In 1927 there was fluttering of the right eyelid, then the right eyelid closed

for five to six weeks, but he could raise it voluntarily a little. Headache off and on till 1927, and ever since then had been continuous.

Examination.—Patient acromegalic in appearance, mandibular prognathism, slight build otherwise. Complains of increasing drowsiness. All movements slow and deliberate, it takes him about one and a half hours to get dressed. Hands enlarged, subcutaneous tissue thickened. Height 5 ft. 9½ in. Weight 126 lb. Blood-pressure 120/80. Urine normal in quantity and quality. Wassermann reaction negative.

The positive neurological findings were as follows: Visual acuity right eye $\frac{6}{6}$ with plus 0·5 lens, left eye $\frac{6}{6}$. Discs normal. Left homonymous hemianopsia. Outward rotation of the eyes normal; inward rotation almost absent, up and down movements very defective. Right pupil larger than left; both react to light and accommodation. A very slight proptosis of the right eye was first noticed in February, 1930. The outlines of the floor of the sella turcica were obliterated and the clinoid processes were widely separated. Resting blood sugar, 0·06 per cent.; after 50 grm. of glucose, 0·09 per cent.

Operation.—March 9, 1930. A trans-sphenoidal operation was performed and some tumour tissue removed. After this operation the patient said that the headache was modified, but was still present. He was treated with deep X-ray therapy, but in the course of two months the headaches returned with greater intensity than ever, and he suffered from extreme photophobia and constant lacrymation.

On June 24, 1930, a right transfrontal exposure of the tumour was attempted but the general intracranial pressure was so extreme that it was impossible to reach the growth in spite of the free use of hypertonic salt solution and glucose. No fluid could be obtained from the ventricles. A large decompression was left. There was but a transient improvement after this operation, and on July 14, 1930, after the administration of hypertonic salt solution and lumbar puncture, a second attempt was made. This proved as futile as the first and had to be abandoned because of the actual bulk of the brain. The patient survived this operation for twenty-one days.

Post-mortem examination.—A tumour about the size of a tangerine orange occupied the peduncular region. The right crus was flattened and appeared twice the width of the left. The right optic tract was flattened out against the crus. The chiasma itself stretched like a bridge between the crura; it was oval rather than flat. The optic nerves were normal in appearance and the tumour had not filled the interval between them.

Microscopic diagnosis: adenocarcinoma.

These cases suggested that normal discs might indicate a retrochiasmal tumour, but the following case showed that normal discs might be found when the tumour was prechiasmal.

Case 6. D. H., male, aged 21. Acromegaly. Headache and vomiting for last year. Diplopia. Normal discs. Bitemporal hemianopsia. Gross enlargement of pituitary fossa. Operation, pituitary tumour. Death. Post-mortem examination, prechiasmal tumour.

The patient was referred to the Richmond Hospital, Dublin, on October 13, 1936, by Dr. Keane, of Belfast, on account of severe headache and vomiting.

The patient began to suffer from headaches accompanied by vomiting a year before admission. About the same time he began to " see double." The headaches steadily increased in severity until they became unbearable. There were occasionally periods of polydipsia and polyuria vaguely remembered.

Examination.—Acromegalic. Height 5 ft. 11 in. Weight 9 st. Blood-pressure 125/60. Basal metabolic rate −12. Mentally dull. Average urinary output was 80 oz. No excessive thirst. Neurological examination negative.

Opthalmological examination revealed normal discs and a complete bitemporal hemianopsia with macular sparing.

The pituitary fossa was grossly enlarged.

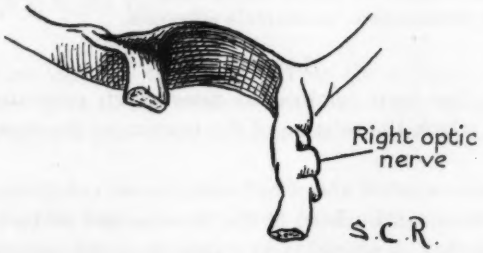

FIG. 10.

November, 1936, he was given a course of deep radiotherapy which had no effect on the headache or vomiting.

January 21, 1937, readmitted in a pitiable condition. The headaches were extremely severe and he had become more sluggish and stupid and occasionally incontinent.

It was decided to make an attempt to relieve the headaches.

March 25, 1937, ventriculography revealed marked dilatation of the lateral ventricles which communicated freely through an opening in the septum lucidum. The 3rd ventricle was not shown.

Operation.—Right transfrontal exposure of the chiasmal region. The right optic nerve was straight and was not displaced laterally. The middle of the pituitary fossa was occupied by a tumour which was attacked by the diathermy loop. A large amount of tissue was removed until the fossa appeared to be empty. The chiasma was not seen. The patient never regained consciousness after the operation and he died eighteen hours afterwards.

Post-mortem examination revealed that the lower third of a column of tumour had been removed and that the upper two-thirds had been left behind.

This upper part of the growth had pushed the chiasma and the anterior wall of the 3rd ventricle backwards and had burrowed into the right frontal lobe just below the genu of the corpus callosum. This depression measured 2½ by 2 cm., and was 2 cm. deep. The chiasma itself was reduced to a mere ribbon, but neither optic nerve was flattened (fig. 10). The right nerve was deeply indented on its upper and lateral aspect by the right anterior cerebral artery. Across the base of the upper surface of the left optic nerve there was a deep groove which seemed to cut the nerve off from the chiasma, leaving only its attachment to the optic tract.

It is noteworthy that gross notching of the optic nerves by vessels did not produce pallor of the discs nor did it seem to account for the defects recorded in the visual fields. Those defects were explained by the chiasmal lesion itself.

Although the tumour in this case was prechiasmal, it differed from the usual type of this tumour in that it did not displace the optic nerves laterally.

Microscopic examination: eosinophile adenoma.

Discussion.

This study has been confined to cases which presented visual field defects and in which the relation of the tumour to the chiasma has been verified.

All the cases reported above had unequivocal symptoms and signs of a tumour in the neighbourhood of the chiasma and all had normal discs. During the period in which these cases were encountered there were eight patients with similarly definite symptoms and signs of tumour in the same situation, in whom there was primary optic atrophy.

In the group with normal discs the optic nerves in each case were normal in appearance and ran straight from the optic foramina to the chiasma. In Cases 1 and 6 the optic nerves had one or more deep notches apparently due to pressure against arteries. These notches were not seen during the operation. In the group with primary optic atrophy, the nerves appeared to be whiter than normal, to be flattened and to curve round the tumour tightly embracing it.

In the first group five of the six tumours were retrochiasmal; the sixth was prechiasmal but of an unusual type.

In the second group all the tumours were prechiasmal.

It would appear that pallor of the discs in cases of tumour in this region is related to displacement or stretching of the optic nerves rather than to any kind of involvement of the optic chiasma or optic tracts, and that the nerves are more likely to be free from embarrassment when the tumour lies behind the chiasma than when it lies in front of the chiasma.

In our experience the meningioma which grows from the tuberculum sellæ is constantly associated with pallor of the discs.

The high proportion of retrochiasmal tumours to prechiasmal in our series calls for comment. In this country slight defects of vision often pass unnoticed by the patient and grave defects are borne with fatalistic equanimity as long as pain is absent. Not one of the patients whose histories are given in this paper, not even the blind one, came to hospital because of failing vision; each came because of pain in the head. Retrochiasmal tumours are more often associated with severe headache than are prechiasmal tumours.

The difference in operative mortality between the two groups is very marked. In the first group with normal discs four out of six patients died. In the group of prechiasmal tumours with primary optic atrophy one patient out of eight died.

Summary.

In five of six cases of tumour involving the chiasma in which the optic discs were normal, the tumour was behind the chiasma. In the sixth case the tumour was of an unusual prechiasmal type.

Conclusion.

When the optic discs in a patient with chiasmal symptoms are pronounced normal by an experienced ophthalmologist, it is probable that the lesion, if a tumour, will be found behind the chiasma.

THE NEURONE AS STUDIED BY MICRO-INCINERATION.

BY LEO ALEXANDER, M.D. (BOSTON, MASS.)[1]

THE micro-incineration method, first conceived by Raspail (1833) developed and perfected by Policard (1923) and Scott (1933, 1933-34), is capable of contributing certain data concerning the structure of the neurone. These data can be divided into three groups :—

(1) Intraneuronal differences in the content of heat-resistant mineral ash.

(2) Interneuronal differences in the content of heat-resistant mineral ash.

(3) Differences in the content of heat-resistant mineral ash exhibited by the same part of the same neurone during different phases of ontogenetic development.

(1) INTRANEURONAL DIFFERENCES.

There are differences in the distribution of the heat-resistant mineral ashes over the various parts of the neurone. The ganglion cells contain considerable mineral deposits in their nucleoli, their cytoplasm and their dendrites (fig. 1). The nucleus is essentially free from mineral residue except for some fine granular strands, especially along the nuclear membrane. The mineral deposits in the cytoplasm are globular and granular in character and correspond in their arrangement to the Nissl bodies. They contain calcium, very little iron, and some water-soluble minerals. The nucleolus, in addition, contains some doubly refractive silica ash. The intracellular neurofibrillæ are completely free from mineral ash (fig. 1). The axone hillock and axis cylinder are completely free of the heavy ash of calcium, iron or silica, and in most well incinerated preparations are free from any heat-resistant mineral ash (Scott, 1933, Alexander and Myerson, 1937). In some specimens, however, here and there some faintly visible

[1] From the Division of Psychiatric Research, Boston State Hospital, and the Department of Neurology, Harvard Medical School, Boston, Mass.

Aided by grants from the Commonwealth of Massachusetts and the Rockefeller Foundation.

mineral granules of bluish colour are seen in the axone hillock and axis cylinder. These granules are soluble in water and are not completely heat resistant because they are usually not present in well incinerated preparations, being vaporized or volatilized at or below the heat of micro-incineration (650° C.).

In the peripheral nerves the axis cylinder either burns out completely or leaves only a faint trace of fine bluish granules, which are vaporized or volatilized easily at higher temperatures. Fig. 2 illustrates these facts in a cross-section from the peripheral nerve of a healthy pigeon. The network of heavy-ash residue corresponds to the endoneural and Schwannian sheaths, the heaviest, white, water-soluble ash

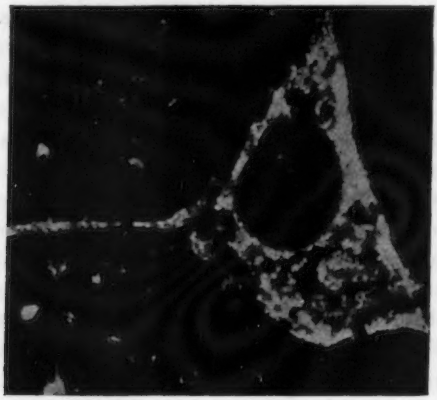

FIG. 1.—Normal motor ganglion cell from anterior horn of spinal cord. Cat. Darkfield illumination. Enlargement × 1300.

residue being that of the nuclei of the Schwannian cells while the endoneural network and the processes of the Schwannian cells, contain somewhat less. A fine, thin, inner layer of much less brightly illuminated ash corresponds to the thin outer membrane of the myelin sheath which is closely adjacent to and, in many places, seems to merge with the cell bodies and processes of the Schwannian cells. The central cores of this honeycombed network, which consists of the endoneural and Schwannian sheaths and at their inner side a thin, outer membrane of the myelin sheath, are occupied, as seen in stained neighbouring sections, by the lipoid body of the myelin sheath, and the axis cylinder. In micro-incinerated preparations, however, the lipoid body of the myelin sheath never leaves

any trace at all; it is always burned out completely without leaving mineral-ash residue. Also the axis cylinder, in many instances, has burned out, thereby leaving the central cores of many meshes of the honeycombed sheath-network completely empty. In other instances, however, either in the centre or somewhat eccentrically in the central core, a small round, elliptic or polygonal body, consisting of an accumulation of fine, faintly visible, bluish mineral granules is seen which corresponds, as stained neighbouring sections show, to the axis cylinder. In some instances, one sees that from the margins of the discs of ash residue, which the cross-sections through the axis cylinders represent, especially from the corners of the polygonal ones, fine threads (2 to 5) of equally faint bluish ash granules extend to the outer membrane of the myelin sheath. These threads, which connect the axis cylinder to the outer membrane of the myelin sheath, are part of the myelo-axostroma of Kaplan (1902). (The myelo-axostroma is not to be mistaken with neurokeratin net, which, especially since Kaplan, has been regarded generally as an artefact.) In some suitable preparations, the observation can be made that those fine ashes, which comprise the trace of the axis cylinder in micro-incinerated preparations, are more dense along the outer membrane of the axis cylinder, the axolemma, than in the interior of the axis cylinder. These findings can best be seen in preparations which are at the border-line of complete incineration. In very thoroughly incinerated preparations, the mineral residue of the axis cylinder is vaporized or volatilized; the ash residue of the myelo-axostroma, however, usually remains.

In the peripheral nerves of the frog, the axis cylinder always burns out completely and is invisible in micro-incinerated preparation. Fig. 3 shows a longitudinal section through the sciatic nerve of the frog. The Schwannian cells are well outlined by their bright white ash residue, as are the endoneural and Schwannian sheaths. All the central cores of the nerve fibres which correspond to the axis cylinders are empty and free from ash residue. The outer parts of these central cores which correspond to the myelin sheaths can be seen transversed by a fine, loose meshwork corresponding to the myelo-axostroma, somewhat heavier threads of which outline the rings of Ranvier and Lantermann's incisures. Several of these are well recognizable in fig. 3. The lipoid part of the myelin sheath contained within the meshes of the myelo-axostroma is free from mineral ash residue.

In the central nervous system in man, axis cylinders usually do not leave any traces in well incinerated preparation. Figs. 4 and 5 show a

part of the optic tract from a 36-year-old man at various enlargements. Most outstanding in their mineral content, consisting for the most part of white water-insoluble ashes, are the nuclei of the glial cells (fig. 4). Somewhat less ash is found in the glial reticulum and in the outer lamellæ of the myelin sheaths. At somewhat higher enlargement, one sees that the lines which the myelin sheaths represent in micro-incinerated preparations are not quite straight or of equal density and calibre, but show numerous varicose excrescences which gives them a somewhat dotted appearance. At still higher power, one recognizes that these highly-mineral containing dots are fibrillary processes of glial cells which pass and adhere to the myelin sheaths at various irregular intervals, embedding them in an irregular network of reinforcements by fibrillary glial processes (fig. 5). These glial reinforcements of the myelin sheaths vary somewhat within the central nervous system. They are most dense and numerous in the central white matter of the hemispheres, less dense in the optic nerve and tract and in the long projection pathways of the brain-stem, while they are of the least density in the white columns of the spinal cord. Their number determines the amount of mineral ash which the white substance presents in micro-incinerated preparations at low enlargement. Compared to the ash content of these glial reinforcements, the outer membrane of the myelin sheath is poor in heat-resistant mineral ash (fig. 5). The central core inside of the outer membrane of the myelin sheath can be seen to be transversed by rather loosely arranged, faintly visible trabeculæ corresponding to the myelo-axostroma. The axis-cylinder itself, and the main lipoid body of the myelin sheath, however, are free from mineral ash. Scott gave a drawing from the sciatic nerve of the cat (fig. 43, plate III), which he did not describe in the text, to which our fig. 5 is very similar.

The musculature is moderately rich in bluish and white, water-soluble and water-insoluble mineral ashes, decidedly less rich than ganglion cells, but much richer than the myelo-axostroma of the nerve fibres. We have not yet been able to identify nerve-endings in micro-incinerated preparations.

In summary it may be concluded:—

(1) Ganglion cells contain rich deposits of heat-resistant mineral ashes in the Nissl bodies of their cytoplasm and their dendrites, and in their nucleolus.

(2) The axone hillocks, the axis cylinder processes, and the main body of the axis cylinders of the central and peripheral nervous system

are completely free from calcium, silica and iron, and are free from other heat-resistant mineral ashes, but contain fine traces of not completely heat-resistant minerals, which are vaporized or volatilized at or below the heat of micro-incineration (650° C).

(3) The myelo-axostroma, including the tubular outer membrane of the myelin sheath, the axolemma, and the connecting threads and lamellæ between them, in the central and peripheral nervous system, contains a small amount of bluish heat-resistant mineral ashes.

(4) The lipoid part of the myelin sheath is always completely free from any mineral ash residue.

(5) The glial reticulum, in which the central nervous structures are embedded, and the Schwannian and endoneural sheaths of the peripheral nervous system, contain moderate amounts of heat resistant mineral ash, the richest accumulation of which is found in the nuclei of glial and Schwannian cells. The glial reticulum in which myelinated nerve fibres are embedded and its ash residue are most dense in the white matter of the hemisphere, less dense in the long projection pathways of the brain-stem, including the optic tract, least dense in the white columns of the spinal cord.

(2) Interneuronal Differences.

Differences in amount and quality of mineral deposits are not only found between ganglion cells of dissimilar morphology, such as between spinal ganglion cells, pyramidal ganglion cells and anterior horn cells (Scott, 1933, Alexander and Myerson, 1937), but also between ganglion cells which are, when studied by the ordinary staining methods, of very similar shape and structure, such as the granular cells of the cerebrum and the cerebellum respectively (Alexander and Myerson). The granular cells of the cerebellum are extremely rich in mineral deposits—calcium as well as iron—while the cortical granular cells from the fourth layer of the isocortex are very poor in mineral residue. This is illustrated by figs. 7 and 8. Fig. 7 shows a section through the central region of the cerebral cortex of a 43-year-old man, including anterior and posterior-central convolutions adjacent to the sulcus centralis Rolandi. The anterior central convolution (a) is extremely rich in white, water-insoluble mineral ash residue, contained in its small and large pyramidal ganglion cells, while the posterior central convolution (p), the ganglion cells of which are of granular type (coniocortex, Economo, 1930), contains comparatively little ash residue. In comparison to the granular cells of the posterior central convolution, however, the granular cells of the

cerebellar cortex from the same individual are very rich in heavy, white mineral ash. This difference does not only apply to the granular layers of the cerebrum and the cerebellum as a whole, but also any single granular cell from the cerebellum is richer in mineral ash than a single granular cell from the cerebral cortex.

This fact can also be well demonstrated in small animals, which present the advantage that one sagittal section through the entire brain can be incinerated on one slide (fig. 6). This eliminates the possible error of difference in thickness and in degree of incineration between different slides. Fig. 6 shows a sagittal section through the brain of a normal adult guinea-pig. The granular layer of the cerebellar cortex is much richer in ash residue than the isocortex of the cerebral hemispheres. The allocortical areas of the fore-brain, however, are much richer in mineral ash than the isocortical areas. Most outstanding in rich mineral content are the cells of the fascia dentata (fd); next are the main allocortical areas at the base of the brain, the tuberculum olfactorium (to), the area prepyriformis (pr), and the area retrobulbaris (rb). (The nomenclature used is that of Rose (1926-27*a*, 1926-27*b*, 1927-28, 1929-30, 1931).) The granular cells of the cerebellum, however, are richer in mineral residue than the cells from the allocortical areas, with the possible exception of the fascia dentata and the area prepyriformis; but this needs furthur investigation by exact quantitative studies. Thalamus and striopallidum are comparatively poor in mineral content. The richer mineral content of the granular layer of the cerebellum, as compared to the cerebral hemispheres and the striopallidum, is also striking in the pigeon and the cat. The granular cells of the cerebellum are not only found richer in mineral residue when completely incinerated, but also are more difficult to incinerate than other ganglion cells. If whole brain sections are incinerated, the cerebellum is the last part to become incinerated completely. This finding points to the fact that other constituents which also determine the speed of incineration, notably proteins, may be of a different nature in the granular cells of the cerebellum, since they more frequently and easily form tarry residues in these than in other cells of the central nervous system. In the cat the area prepyriformis (pr) is outstandingly rich in white mineral ash as compared to the isocortical areas, for example the area precentralis granularis (pg), in the same section (fig. 9). In the olfactory bulb, the cells of the inner granular layer are richer in mineral residue than those of the outer granular layer (fig. 9 bu); the stratum granulosopyramidale (pyramidale internum) and the stratum pyramidale

externum contain much less; the inner and outer molecular layers are practically free from heat-resistant mineral ashes. This distribution of the heat-resistant mineral ashes in the olfactory bulb is positively correlated with the depth of colouring which these layers present in Nissl-stained preparations (compare our fig. 9 to corresponding Nissl-stained preparations given in Rose's atlas).

These differences in heat-resistant mineral ash exhibited by the various types of neurones in the central nervous system of man and animals will have to be studied in more detail by methods which permit a more accurate qualitative and quantitative analysis. These data, gained by micro-incineration, give a lead in this direction. Especially the constancy of greater ash content of cerebellum and allocortex, as compared to isocortex, thalamus and striopallidum throughout the phylogenetic series, is of interest and may bear a certain relationship to functional constancy.

(3) Differences in the Content of Heat-resistant Mineral Ash Exhibited by the same part of the same Neurone during Different Phases of Ontogenetic Development.

Embryonic tissue, as well as tumour tissue, is richer in heat-resistant mineral ash than normal differentiated adult tissue (Horning and Scott, 1932; Scott and Horning, 1932; Alexander and Myerson, 1937). For the neurones of the human central nervous system, Alexander and Myerson have demonstrated that the cortical ganglion cells of the new-born child are richer in heat-resistant mineral ash than those of the adult; most of this ash, however, is contained in the nuclei of the ganglion cells of the new-born, while their cytoplasm contains only small amounts of it (Alexander and Myerson, plate lxiii, fig. 1). Differences of the ash content in the various cortical areas during ontogenetic development have been studied in a series of brains from the fœtal and the new-born cat and of kittens during the first three weeks of life. Sagittal sections were cut in order to be able to incinerate as many different parts of the brain as possible on one slide at the same time. Fig. 10 shows an incinerated sagittal section through the entire brain of the new-born cat at low enlargement. The cerebellar cortex and various areas of the allocortex, notably the cornu ammonis (c), the area entorhinalis (e) and the area prepyriformis (pr), stand out by their rich ash content, as they do in the adult: but, in addition, two areas of the isocortex are well and sharply outlined by their exceedingly rich

content of heat-resistant mineral ash, namely, the area striata (str) and the anterior central region (ac). These two areas are in the process of most active growth at that time, and they are the first two areas of the isocortex to undergo myelinization (primordial areas) (Flechsig, 1901, v. Monakow, 1914). According to Flechsig, myelinization occurs first in the central region, second in the fascia dentata, the uncus gyri hippocampi and other allocortical regions, third in the cornu ammonis, fourth in the area striata. In the newborn cat, also, the thalamus and the striopallidum are relatively richer in heat-resistant mineral ash than in the adult.

Within the same area, and within the same type of neurone, the more primitive cells are richer in heat-resistant mineral ash than those which have already reached higher differentiation. This fact is best illustrated in the cerebellar cortex of the newborn, mammalian as well as human, owing to a peculiarity of the topographic arrangement of its still-proliferating primitive, and its differentiated cells, which has been well described by Ramón y Cajal (1890*a*), Lugaro (1894*a*), Schaper (1894), Biach (1909-10), Löwy (1909-10) and Obersteiner (1912).

The matrix of the cerebellar cortex, at about the middle of embryonic life in man, splits in an outer and an inner granular layer, separated by the anlage of the molecular layer. While the cells of the inner granular layer undergo early differentiation and cease to proliferate, the cells of the outer granular layer at the outer surface of the cerebellar convolutions retain their primitive medullo-blastic character up to the eighth or ninth month of intrauterine life, continue to proliferate and to supply, among other cells, additional neuroblasts which continuously migrate through the molecular layer into the inner granular layer where they undergo differentiation into cerebellar granular cells. Thus, for a long period, the outer granular layer remains the matrix (secondary matrix) of the granular layer of the cerebellar cortex, consisting of undifferentiated, actively proliferating cells, while the differentiated cells accumulate in the inner granular layer. In the newborn, these two layers are clearly separated by the intervening molecular layer (Obersteiner, fig. 232, page 611). In micro-incinerated preparations of the cerebellum of the newborn cat, as well as of the newborn human infant (fig. 11), the immature outer granular layer (og) is much richer in heat resistant, water-insoluble mineral ashes than the mature, differentiated, inner granular layer (ig). Not only the outer granular layer as a whole, but each individual cellular element of the primitive outer granular layer is richer in white, brightly luminous ash than the

individual differentiated cellular elements of the inner granular layer. This finding justifies the conclusion that neurones during active growth and ontogenetic development are relatively richer in heat resistant mineral ashes than after differentiation.

Conclusions and Summary.

(1) Ganglion cells contain rich deposits of heat resistant mineral ashes in their nucleolus and in the Nissl bodies of their cytoplasm and dendrites.

(2) The intracellular neurofibrillæ, the axone hillock and the main body of the axis cylinder are free from heat-resistant mineral ashes.

(3) The lipoid part of the myelin sheath is free from mineral ash.

(4) The myelo-axostroma contains a small amount of heat-resistant mineral ash.

(5) The granular cells of the cerebellar cortex and the ganglion cells from allocortical areas are richer in mineral ash residue than morphologically similar ganglion cells from isocortical areas or from the basal ganglia. In addition, there is a great deal of variation in the mineral distribution corresponding to cortical architectural fields.

(6) The content of heat-resistant mineral ash in the same neurone is relatively greater during ontogenetic development than after differentiation.

(7) The fact that the content in heat-resistant mineral ashes is greater in ganglion cells than in nerve fibres, and relatively greater in ganglion cells during ontogenetic development than after differentiation, suggests a positive correlation of these heat-resistant mineral ashes with growth and with metabolic activity.

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PLATE II.

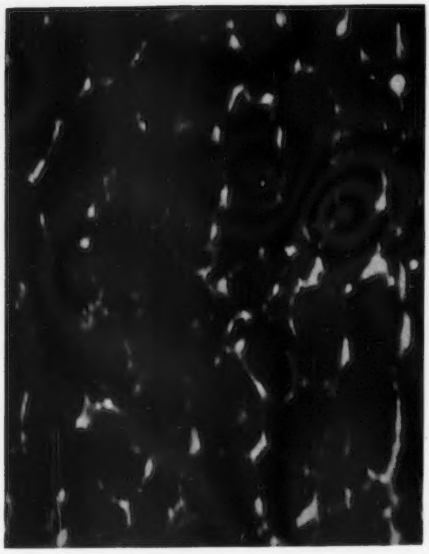

FIG. 2.

FIG. 4.

FIG. 3.

FIG. 5.

To illustrate paper by Leo Alexander.

PLATE III.

FIG. 6.

FIG. 7.

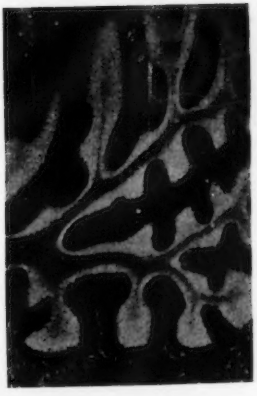

FIG. 8.

FIG. 9.

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PLATE IV.

FIG. 10.

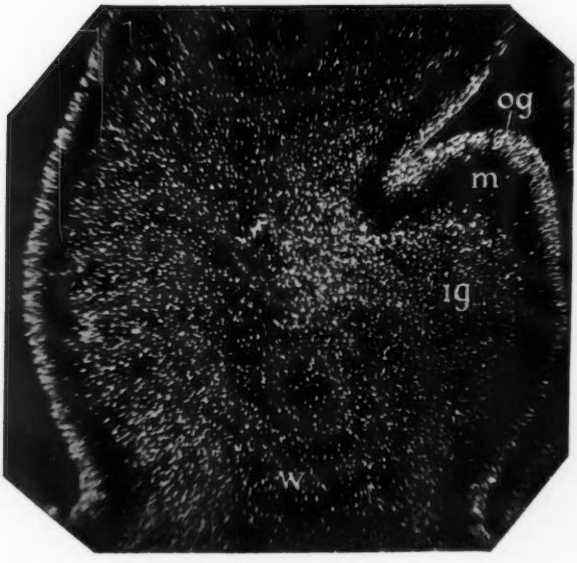

FIG. 11.

To illustrate paper by Leo Alexander.

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LEGENDS.

Fig. 2.—Transverse section through peripheral nerve (wing nerve) of a healthy pigeon. Darkfield illumination. Enlargement × 1300.

Fig. 3.—Longitudinal section through peripheral nerve (sciatic nerve) of a frog. Darkfield illumination. Enlargement × 1300.

Fig. 4.—Longitudinal section through the optic tract of a 36-year-old man. Darkfield illumination. Enlargement × 175.

Fig. 5.—A myelinated fibre from the optic tract shown in fig. 4 at higher enlargement. Darkfield illumination. Enlargement × 2210. c = central core of the nerve-fibre, occupied by the axis cylinder and the inner lipoid part of the myelin sheath, which are free from mineral ash residue. In the lower half of the figure the central core of the nerve-fibre is seen to be transversed by a few fine threads which are part of the myelo-axostroma.

Fig. 6.—Sagittal section through the brain of a normal guinea-pig. Oblique transillumination. Enlargement × 7. fd = fascia dentata, pr = area prepyriformis, rb = area retrobulbaris, to = tuberculum olfactorium.

Fig. 7.—Section through the anterior and posterior central convolutions of the normal human cerebral cortex and the intervening sulcus centralis Rolandi. 43-year-old man. Oblique transillumination. Enlargement × 8. a = anterior central convolution, p = posterior central convolution.

Fig. 8.—Section through normal cerebellar convolutions. 43-year-old man. Oblique transillumination. Enlargement × 8.

Fig. 9.—From a sagittal section through the brain of a newborn cat. Oblique transillumination. Enlargement × 7. bu = olfactory bulb, pg = area precentralis granularis, pr = area prepyriformis.

Fig. 10.—Sagittal section through the brain of a new-born cat. Oblique transillumination. Enlargement × 7. ac = anterior central region, c = cornu ammonis, e = area entorhinalis, pr = area prepyriformis, str = area striata.

Fig. 11.—Convolutions of the cerebellum of the new-born human infant. Darkfield illumination. Enlargement × 80. ig = inner granular layer, m = anlage of the molecular layer, og = outer granular layer, w = central white matter of cerebellar convolution.

THE ORIGIN OF THE FALL IN THE PRESSURE OF THE CEREBROSPINAL FLUID AFTER ITS ARTIFICIAL ELEVATION BY JUGULAR OCCLUSION.

BY T. H. B. BEDFORD.

(From the Department of Pharmacology, Manchester University.)

THE effect of jugular occlusion on the cerebrospinal fluid pressure in the cisterna magna and on the venous pressure in the torcular has been described in earlier papers (Bedford, 1935, 1936). It was found that the rise in the pressure of the cerebrospinal fluid which follows sudden occlusion of the external jugular veins is a temporary phenomenon, and that the pressure usually returns to the region of its original level within the space of one hour. The venous pressure in the torcular was also observed to fall, but the fall was not so rapid or so complete as the fall in the pressure of the cerebrospinal fluid, and at the end of the experiment the torcular venous pressure was sometimes more than twice its original height. These pressure changes were found to occur independently of variation in the systemic arterial pressure. The average duration of the experiments was two hours. It was concluded that the fall in the pressure of the cerebrospinal fluid was due mainly to the establishment of collateral venous circulation. It was considered, however, that there had been also a reduction in the total volume of the cerebrospinal fluid. In the experiments which are to be described, an attempt has been made to study the problem by observing the effect of jugular occlusion on the rate of absorption of isotonic solution from the subarachnoid space.

EXPERIMENTAL PROCEDURE.

The general experimental procedure and the methods employed to record the intracranial pressures were identical with those used in earlier experiments (Bedford, 1935, 1936). The manometer in the cisterna magna was, however, connected by a three-way tap with a device by which the pressure of the cerebrospinal fluid could be maintained at any desired level and the rate of inflow or of outflow of fluid from the subarachnoid space determined. The apparatus employed for this purpose was modelled on that used by Mortensen and Weed (1934)

in their study of the absorption of isotonic solution from the subarachnoid space. These workers have given a detailed description, including a diagram of their apparatus. It is unnecessary, therefore, to give more than a brief account here. The apparatus consists of a reservoir of large diameter, containing isotonic saline solution, which can be raised or lowered. The diameter of the reservoir is sufficiently large to ensure that the maximum volume of fluid likely to enter or to be expelled from the subarachnoid space during the period of an experiment will have no appreciable effect on its fluid level. The pressure of the cerebrospinal fluid can, therefore, be maintained at any desired level by setting the reservoir and putting it into communication with the needle in the cisterna magna. A device consisting of two vertical graduated pipettes is interposed between the reservoir and the three-way tap. The upper half of each pipette and the connecting tubing is filled with a paraffin-chloroform mixture coloured with Sudan III. This mixture has the same specific gravity as the saline solution. The volume of fluid passing from the external system into the animal or extruded under conditions of constant pressure can be determined by observing the meniscus between the paraffin-chloroform mixture and the saline solution. The oily mixture may occasionally stick to the sides of the pipettes or retract unevenly during rapid extrusion or inflow of fluid, and thus render accurate reading impossible. Two pipettes are employed merely to ensure that one meniscus at least is available for reading. The only modification introduced into this apparatus has been the replacement of rubber connections by glass where possible. The saline solution used in these experiments was Tyrode's solution.

(1) *The effect of jugular occlusion on the absorption of isotonic solution from the subarachnoid space when the reservoir is set at the pressure level assumed by the cerebrospinal fluid.*

The normal pressure of the cerebrospinal fluid and the venous pressure in the torcular were first determined. The external jugular veins were then occluded and the new pressure levels noted. After a preliminary pause of some two or three minutes, the reservoir was set at a pressure corresponding with that of the cerebrospinal fluid and put into communication with the subarachnoid space. The rate of inflow or of outflow of fluid was observed over a period of one to one and a half hours. Fifteen experiments were performed. A fairly typical experiment is represented in fig. 1. The relative stability of the venous pressure after the pressure of the cerebrospinal fluid had once been

fixed was a striking feature of these experiments. The venous pressure in the torcular at the end of the experiment was often identical with that observed at the beginning. A pronounced fall in venous pressure was generally associated with a fall in the systemic blood pressure and

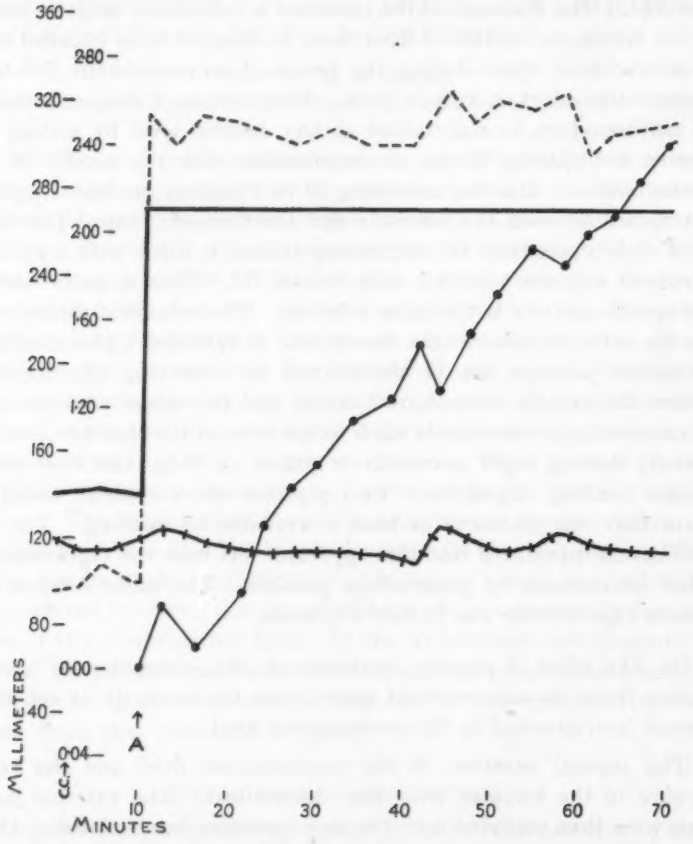

FIG. 1.—The effect of jugular occlusion on the absorption of cerebrospinal fluid when the reservoir is set at a pressure level corresponding with that assumed by the cerebrospinal fluid. The pressure of the cerebrospinal fluid and the torcular venous pressure are recorded in millimetres of Tyrode solution, that in the femoral artery in millimetres of mercury. The external volume is recorded in cubic centimetres of Tyrode solution. The veins were occluded and the cerebrospinal fluid pressure maintained at A.

———— Cerebrospinal fluid pressure.
– – – – – Venous pressure in torcular.
—•—•— External volume change.
—+—+— Systolic pressure in femoral artery.

an experiment was not considered successful unless the systemic arterial blood-pressure was maintained. A flow of fluid from the external system into the animal was observed in all experiments. This persisted even when the venous pressure rose, although sudden changes in the venous pressure were temporarily reflected in the rate and occasionally in the direction of flow. The average rate of flow in fifteen experiments was 0·049 c.c. per minute. In some of the experiments, however, there was a moderate fall in the venous pressure in the torcular. This would bring about a decrease in the total volume of the intracranial venous system and cause a flow of fluid from the reservoir into the animal. The rate of inflow was accordingly relatively greater in these experiments than in those in which the venous pressure was maintained.

(2) *The effect of jugular occlusion on the absorption of isotonic solution when the pressure of the cerebrospinal fluid is maintained at its original level.*

The pressure of the cerebrospinal fluid was first recorded until its level became reasonably steady. The reservoir was then set at that level and put into communication with the subarachnoid space. Under these circumstances fluid should neither enter nor be expelled from the subarachnoid space, although minor fluctuations may be observed. Twelve experiments were performed. On occluding the external jugular veins, fluid was rapidly displaced from the subarachnoid space into the external system. This displacement of fluid lasted sometimes for one to three minutes. The volume of fluid displaced during this period averaged 1 c.c. It is interesting to recall that Mortensen and Weed found that an average introduction of 1·30 c.c. of saline into the subarachnoid space was necessary in order to double the pressure of the cerebrospinal fluid. The external volume remained constant after this initial displacement of fluid, save for minor fluctuations, in half the experiments. In the other half, fluid was steadily extruded into the external system. The maximum average rate of outflow observed in any one experiment was 0·023 c.c. per minute. Jugular occlusion was followed by a rise in the venous pressure in the torcular. The rise in pressure was, however, less than that observed when the escape of fluid from the subarachnoid space was prevented. This observation is in harmony with earlier findings (Bedford, 1936). In ten experiments the increase in the venous pressure averaged 150 mm. saline solution. The venous pressure was therefore rarely twice that of the cerebro-

spinal fluid. It was noted that, except for minor fluctuations, the venous pressure in the torcular usually remained steady throughout the experiment. It would appear, therefore, that the effect of jugular occlusion was to cause a rapid initial displacement of fluid from the subarachnoid space. This was followed in half the experiments by a steady extrusion of fluid which, however, never averaged more than 0·023 c.c. per minute. In the remaining experiments there was no evidence of inflow or of outflow of fluid and the external volume remained unchanged.

(3) *The rate of absorption of isotonic solution when the reservoir is set at a pressure level equal to twice that of the cerebrospinal fluid and the jugular veins are not ligated.*

Jugular ligation generally causes the pressure of the cerebrospinal fluid to be approximately doubled. It was decided to determine the rate of absorption of isotonic solution when the reservoir is set at a pressure twice that of the cerebrospinal fluid and the jugular veins are not occluded. Four experiments in all were performed. An average rate of absorption of 0·062 c.c. per minute was obtained. This figure is somewhat higher than that found by Mortensen and Weed, who obtained an average rate of absorption of 0·054 c.c. per minute in thirteen experiments.

Discussion.

The experiments on the effect of jugular occlusion on the absorption of isotonic solution when the reservoir is set at the pressure assumed by the cerebrospinal fluid would appear to indicate that (1) the return of the pressure of the cerebrospinal fluid to normal after ligation of the external jugular veins is brought about by a diminution of the total volume of the cerebrospinal fluid; (2) the fall in the venous pressure in the torcular is mainly dependent on the fall in the cerebrospinal fluid pressure. According to Weed and co-workers (1934, 1935-36) the cerebrospinal fluid is absorbed by a process of simple filtration through the arachnoid villi. Weed considers that "the total effective pressure activating the normal process of absorption of cerebrospinal fluid is compounded of the colloid osmotic pressure of the blood plus a hydrostatic factor derived from the difference in the subarachnoid pressure and the intracranial venous pressure." Weed (1935) states that the colloid osmotic pressure of the blood lies between 250 and 300 mm. saline solution. If these conclusions are correct, the absorption of the

cerebrospinal fluid in the experiments under consideration may be expected to proceed at a markedly reduced rate in the most congested parts of the subarachnoid space. Jugular ligation generally causes the venous pressure in the torcular to equal or exceed slightly the pressure assumed by the cerebrospinal fluid. Normally the pressure of the cerebrospinal fluid is slightly higher than the venous pressure in the torcular. It would appear, however, from a consideration of the anatomy of the intracranial venous system of the dog (Bedford, 1934), that the venous pressure will probably be highest in the superior longitudinal, the straight and the lateral sinuses. In the remaining sinuses the pressure will be undisturbed or very slightly raised. Weed has shown that the cavernous sinus is particularly rich in arachnoid villi. In this region and in the subtentorial and spinal portion of the subarachnoid space, cerebrospinal fluid will be absorbed at a rate corresponding roughly with that observed when the pressure of the cerebrospinal fluid is doubled. The average rate of inflow in fifteen experiments was 0·049 c.c. per minute. This figure is slightly lower than that obtained when the pressure of the cerebrospinal fluid was doubled and the external jugular veins were not occluded. As already stated, however, a moderate fall in venous pressure occurred in a number of the experiments. This was invariably accompanied by an increased rate of inflow of fluid and is no doubt partly responsible for the relatively high figure. Nevertheless, it must be admitted that the rate of absorption in these experiments was greater than expected. The intracranial venous congestion involved the main areas in which absorption is generally supposed to take place. A more pronounced reduction in the rate of absorption was anticipated on the basis of Weed's theory of the absorption of cerebrospinal fluid. It is apparent that this aspect of the subject is in need of further study.

A diminution in volume of the cerebrospinal fluid may be brought about by a diminution in rate of production while the rate of absorption remains unchanged, or by an increased rate of absorption while the rate of production remains unchanged. It is also conceivable that a state of increased absorption may be accompanied by one of diminished production. We have as yet no precise knowledge concerning the effect of changes in the venous pressure on the formation of cerebrospinal fluid by the choroid plexuses. The results of the experiments on the effect of jugular occlusion on the absorption of isotonic solution when the pressure of the cerebrospinal fluid is maintained at its original level would appear to suggest that the raised venous pressure did not cause the production of

cerebrospinal fluid to be diminished. It is, however, doubtful to what extent this conclusion is justifiable. The extrusion of fluid observed in half the experiments may have been caused in any of the following ways: (1) The reservoir may have been set at a lower pressure level than the true pressure of the cerebrospinal fluid. Stringent precautions were, however, taken to determine the normal level of the cerebrospinal fluid at the start of all experiments; (2) there may have been an increased production of cerebrospinal fluid; (3) the outflow of fluid may have been the result of a diminished rate of absorption into the venous sinuses; (4) the venous pressure in these experiments was raised suddenly, the resistance to vascular dilatation normally opposed by the raised pressure of the cerebrospinal fluid was almost entirely absent and fluid was displaced freely from the subarachnoid space. It is possible, therefore, that a condition of œdema and vascular dilatation was set up in the nervous system. The effect of rapid drainage of cerebrospinal fluid on the blood vessels of the central nervous system has been studied in detail by Masserman (1934, 1935). The outflow of fluid in the experiments under consideration may therefore have been caused in part by a spreading œdema and vascular dilatation of the central nervous system.

To sum up, it would appear that the return of the pressure of the cerebrospinal fluid to normal after ligation of the external jugular veins is caused by a diminution in volume of the cerebrospinal fluid. This decrease in volume of the cerebrospinal fluid may be brought about by an increased rate of absorption in those parts of the subarachnoid space which are least affected by the raised venous pressure. The fall in the venous pressure in the torcular would seem to depend mainly on the fall in the pressure of the cerebrospinal fluid.

Summary.

An attempt has been made to discover the cause of the return of the pressure of the cerebrospinal fluid to normal after its artificial elevation by jugular occlusion. A study was made of the effect of jugular ligation on the absorption of isotonic solution from the subarachnoid space. It was concluded as a result of these experiments that (*a*) the return of the pressure of the cerebrospinal fluid to normal after jugular occlusion is due to a diminution in the volume of the cerebrospinal fluid; (*b*) this diminution in volume may be brought about by increased absorption in those parts of the subarachnoid space which are least influenced by the

raised venous pressure; (*c*) the accompanying fall in the venous pressure in the torcular is mainly dependent on the fall in the pressure of the cerebrospinal fluid.

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VASCULAR LESIONS IN THE BRAIN-STEM AND OCCIPITAL LOBE OCCURRING IN ASSOCIATION WITH BRAIN TUMOURS.[1]

BY MATTHEW T. MOORE (PHILADELPHIA) AND KARL STERN (LONDON).

THE study of vascular lesions occurring in brains which are the seat of tumours, using this word in the broad sense of space-taking lesions, is important from several points of view. Firstly, their appearance complicates the clinical picture and produces difficulties in diagnosis. Secondly, an investigation of their pathogenesis may assist in the general problem of intracranial circulation in relationship to lesions producing increased intracranial pressure.

Hæmorrhages in the lower brain-stem were first studied in connection with traumatic cerebral lesions. Duret (1919-20) described multiple small hæmorrhages in the region of the aqueduct and the floor of the 4th ventricle, which he thought were produced by a sudden increase in the local cerebrospinal pressure. In some instances these lesions appear some time after the original cerebral trauma ("Spät apoplexie"—Bollinger). Kolisko (1911) abandoned Duret's explanation of the pathogenesis of the hæmorrhagic lesions and advanced the theory of the greater vulnerability of the basilar artery and its branches from a mechanical point of view. The earliest comprehensive survey of the problem of brain-stem hæmorrhage, was made by Attwater (1911) from cases of cerebral apoplexy and trauma. In 67 cases he found an accompanying pontine hæmorrhage in 30 per cent., mostly in cases where the cerebral hæmorrhage was large and had ruptured into the ventricle. He expressed the opinion that the pontine hæmorrhage was secondary to the cerebral hæmorrhage. In one case, however, where there was a large pontine hæmorrhage and a small hæmorrhage in the internal capsule, he felt that the pontine hæmorrhage was the primary one.

In a special study of spontaneous multiple cerebral hæmorrhages, Greenacre (1917) found the combination of a cerebral and pontine hæmorrhage in 63 per cent. of cases studied. She suggested that in these cases a "friction" must occur between the two channel beds, the

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carotid and the vertebral, and, "since the meeting takes place in the posterior part of the system, owing to the greater length and more circuitous route of the vertebrals, the pressure throughout the basilar is presumably increased above that in the other arteries, and its branches are subjected to unusual strain."

Wilson and Winkelman (1926) recorded a comparative study of 13 cases of pontine hæmorrhages occurring in 129 autopsies, which included 26 cases of trauma, 40 of vascular disease, 52 of neoplasm and 11 of abscess. Of the 13 cases of pontine hæmorrhages only 4 were associated with the lesions we are here concerned with, namely 3 neoplasms and 1 abscess. Their explanation of the causative factors, like that of Kolisko, was that the increased intracranial pressure pushed the pons against the base of the skull. They also suggested that "in the traumatic cases it is probable that the upper pons transmits the impact from one hemisphere to the other, and thus may be injured indirectly."

In a series of sixteen cases of brain tumour, Rosenhagen (1932) found ten (62·5 per cent.) in which multiple pontine and tegmental hæmorrhages occurred. He regarded these hæmorrhages as analogous with the hæmorrhages occurring in trauma and as due to sudden changes in cerebrospinal fluid pressure. He ascribed the situation of these hæmorrhages to the exposed position of the basilar artery.

The problem also was taken up by Bannwarth (1935). He found hæmorrhage in 4 temporal and 1 frontal lobe tumours, and taking into account Rosenhagen's 6 temporal, 2 parietal, 1 hemispheric, and 1 frontal lobe tumours, concluded that temporal lobe tumours have a greater tendency than others to produce these lesions. In his cases no causal relationship with operation could be shown, as only one case had been operated upon. In explanation he adopts the general theory of Albert, viz., as the blood-pressure falls gradually from the arteries to the capillaries and from these to the veins the rising intracranial pressure must act first on the veins as the point of least resistance. If the intracranial pressure rises sufficiently to compress the veins while the arterial flow is still maintained, congestive arterial hyperæmia, excessive engorgement of the capillaries, and, finally, arterial hæmorrhage by diapedesis and by rhexis must occur. If acute brain swelling occurs in tumours the resulting increased pressure first acts upon the region offering least resistance, i.e. the foramen magnum and the lower brain-stem, compressing the veins in that area and producing arterial congestive hyperæmia and hæmorrhage in the described way.

Stern (1933) pointed out that in diseases with increased intracranial pressure other than tumours, e.g. cerebral injury, renal disease, and heatstroke, the arteries in the posterior fossa seem to be exposed to an unusual strain and are more liable to disturbances than the arteries in other areas of the brain. In a case of heat-stroke he described symmetrical softenings in the lower brain-stem and hypothalamus, in both occipital poles and in the left hippocampus. There was a separation of the intimal layer of the extracerebral arteries supplying these areas and blood was found between the intima and media. Apparently this had happened in previously healthy arteries. Finally, Adolf Meyer (1920), in his paper on "Herniation of the Brain," described one case of cerebral tumour in which compression of the posterior cerebral artery had caused an infarction of the occipital lobe.

Material and method.—One hundred and thirty brains in which brain tumour or abscess was present were examined for evidences of vascular lesions. Of these the first hundred were from a consecutive series of autopsies, and 14, or 14 per cent., showed accompanying vascular lesions either in the pons, mid-brain or occipital lobe. In addition to these 14 cases, 4 showing vascular lesions were examined among the remaining 30 brains of the entire group. Five of the total of 18 cases of hæmorrhage cases presented the gross appearance of occipital lobe infarction. Fourteen cases were studied histologically in frozen and celloidin sections with Nissl, Hæmatoxylin-Van Gieson and Herxheimer-Sharlach R stains. The basilar artery and its branches and the posterior cerebral and its calcarine branches were dissected out, embedded in paraffin and studied with Hæmatoxylin-Van Gieson and Weigert's Elastica stains.

To Dr. J. Godwin Greenfield we are indebted for the privilege of using this material and for his autopsy reports, and to the honorary physicians of the National Hospital, Queen Square, for permission to review the following case reports.

Calcarine Infarction.

Case 1.—E. B. (Case No. 67/37), female, aged 43 (Dr. Gordon Holmes), was admitted to hospital on March 1, 1937, complaining of weakness of the left arm and left leg. She had enjoyed her usual health until one week before entering hospital. On February 25, 1937, she yawned the greater part of the afternoon and was very drowsy. She had difficulty with her speech, and found her left arm weak. On February 27 her left arm had become useless and she noticed that she was dragging the left leg. There was no pain or headache associated with these symptoms.

The past medical history and family history were irrelevant.

Examination.—She showed a definite organic dementia and marked stammer and was unable to carry out elementary mathematical problems. There was no evidence of field defect and the optic discs were normal. The pupils were irregular and unequal in size, completely inactive to light but reacted well on convergence. There was marked bilateral ptosis. There was hypalgesia on the nose and cheek, more pronounced on the right side. The

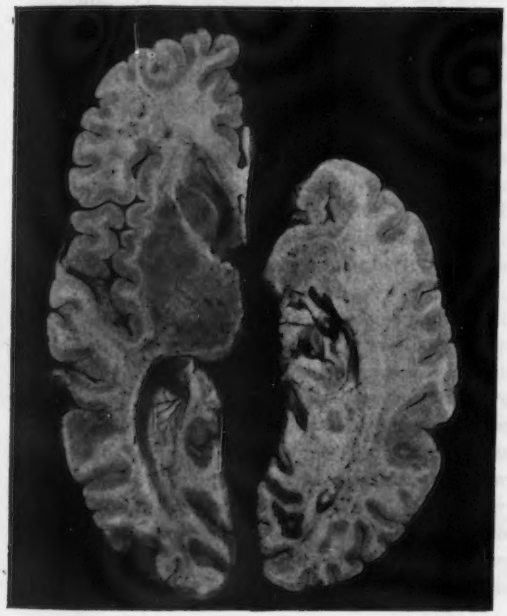


FIG. 1.

FIG. 2.

FIG. 1.—*Case* 1. Bilateral infarction of the calcarine cortex in a case of tumour of the right basal ganglia.

FIG. 2.—*Case* 1. Laminar softening of the cortex. There is a clear demarcation between the first two layers which are fairly well preserved and the remaining layers which bear the brunt of the softening. (Cresyl violet—low power.)

corneal reflex was more active on the right than on the left. She showed left lower facial weakness. The other cranial nerves were normal. There was definite left hemiparesis, more pronounced in the upper limb and accompanied with a moderate degree of hypertonus. There was a slight hypalgesia over the thorax and inner border of the upper limbs.

On March 2, 1937, lumbar puncture gave a clear cerebrospinal fluid under 120 mm. water pressure. There were no cells, total protein was 0·18 per cent. During the patient's stay in hospital her mental and neurological abnormalities became more marked. On March 30, she showed a paresis of conjugate

movements of the eyes upwards. Slight papillœdema first appeared on April 11 but was not definite until May 6. She had periods of unconsciousness from May 16 to the time of her death on June 12, 1937.

Post-mortem examination.—The examination of the viscera was negative.

Brain: The arteries were healthy. There was no swelling of the pons, mid-brain or convolutions. On examining the thalamus on the two sides after incision of the corpus callosum, that on the right was definitely bulkier than that on the left. On incision here a rounded mass of tumour with ill-defined edges was seen just under the ventricular surface of the thalamus, and this was found to extend downwards into the right side of the mid-brain.

In the *calcarine region*, on both sides, the cortex was shrunken, soft, and of reddish-brown colour. The change was not limited to the area striata only but also extended to the area parastriata. The cortical involvement on the left side was more extensive than on the right (fig. 1). However, in some cross sections the lesions appeared almost symmetrical. The white matter adjacent to the involved area was somewhat soft and shrunken but did not show any abnormal colour. The vessels supplying the areas described appeared quite normal macroscopically.

Histological examination.—In the right occipital cortex (areæ striata and parastriata) the ganglion cells of several gyri had entirely disappeared and had been replaced by a glial proliferation and new vessel formation. The first two cortical layers appeared fairly well preserved but the remaining layers were severely involved (fig. 2). There was considerable proliferation of glial elements, consisting of macroglia and "gemästete" glia. In addition, there was an extensive capillary proliferation, segregation of capillary endothelium, and "gitter" cell formation; the white matter only showed a slight diffuse glial reaction. The left occipital cortex presented the same histological appearance. The pial vessels in the areas studied were normal. The dissected isolated occipital and pontine vessels were normal histologically.

Calcarine Infarction.

Case 2.—A. S. (Case No. 39/35), male, aged 44 (Dr. James Collier), was admitted to hospital on February 21, 1935, complaining of headaches and confusion in speaking. In September of 1934, during an attack of influenza, he noticed that his memory was poor. Since that time he had persistent headache, chiefly in the evening. During October, 1934, he developed difficulty in writing and speaking. He lost interest in his family and his business.

Examination.—The patient was emaciated. There was a difficulty in speech and his attention was poorly sustained. The nasal halves of both discs were blurred, but no definite swelling was visible. There was slight bilateral ptosis. Movement of the right upper lip was somewhat weak. The other cranial nerves were normal. Motor function and sensation could not be properly evaluated because of lack of co-operation. The reflexes showed no abnormal responses. The blood-pressure was 130 systolic, 90 diastolic. The blood-count was normal.

A ventricular puncture performed February 26, 1935, showed the following: Initial pressure 300 ++ mm. water, clear, colourless fluid, 4 cells, total protein 0·08 per cent., Nonne-Appelt +, Pandy +, Lange negative.

Post-mortem examination.—Brain only examined. The skull was thinned showing convolutional markings. This was more marked in the region of the left parietal eminence where the inner aspect of the bone was redder and rougher than on the right, and the middle meningeal furrow was obliterated. The left temporal lobe was attached to the dura over the outer aspect of the pole, and here a large firm tumour was found coming to the surface. There was a yellowish degeneration in its mesial aspect.

There was considerable absorption of the bone in both middle cranial fossæ, especially the left. The floor of the sella was a very thin shell of bone and the posterior clinoid processes were almost completely destroyed.

Examination of the brain after fixation showed a very marked herniation of the left uncus through the incisura tentorii, and a fairly deep notch with underlying bruising was found on the outer surface of the right crus.

At the margin of the *left calcarine fissure* the cortex was thinned, was reddish in colour, and appeared to be softer than normal. The pons and mid-brain showed no change.

Histological examination.—In the affected calcarine area no nerve-cells could be seen, but the glia cells, especially microglia, were swollen and increased in number. The vessels were proliferated and the capillary wall elements were also swollen. There was considerable " gitter " cell formation.

The extracerebral vessels, both arteries and veins, in the involved area appeared normal.

Calcarine Infarction and Pontine Hæmorrhage.

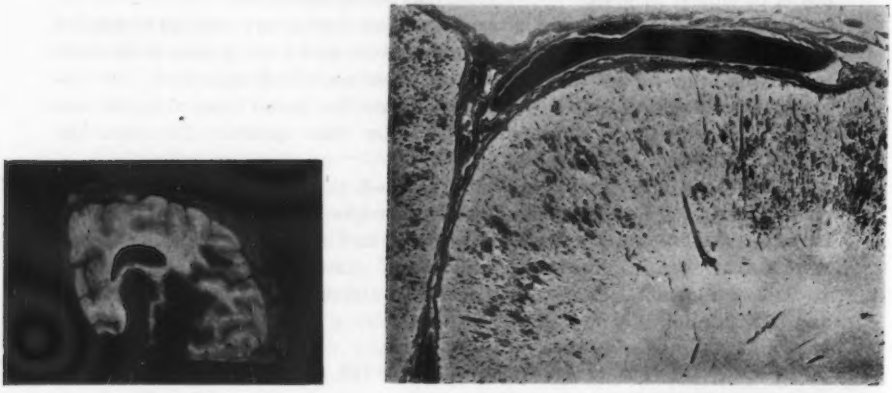
Case 3.—A. H. (Case No. 47/34), male, aged 31 (Dr. C. P. Symonds), was admitted to hospital on April 4, 1934, complaining of pains in the eyes and headache. These complaints had been present for four months. For one and a half years he had had pains over the front of the left side of his chest. There had been tingling in the legs for a few days. He had had one attack of vomiting three weeks before admission.

Examination.—There was a bilateral papillœdema of three to four dioptres. The remaining cranial nerves were normal. The reflex activity showed no gross abnormalities. The gait was unsteady. All forms of sensation were normal. The blood-pressure was 150 systolic, 80 diastolic.

Lumbar puncture performed April 9, 1934, showed an initial pressure of 300 + mm. water. The cerebrospinal fluid was normal. The patient had severe headache following the puncture, but then remained fairly well until April 12, when he could not be roused. The corneal reflexes became very sluggish, and the pupils were fixed to light stimulation. The pulse dropped from 64 to 52. 100 c.c. of 50 per cent. glucose administered intravenously produced no improvement. The right lateral ventricle was tapped in the ward on April 12 and 100 c.c. of cerebrospinal fluid removed. The ventricular fluid

was normal. The patient remained unconscious. A posterior fossa decompression was performed under general anæsthesia. The dura was not under abnormal tension and on opening the dura the cisterna magna was considerably distended with cerebrospinal fluid. There was no herniation of the cerebellar tonsils. The patient died on the day of operation.

Post-mortem examination.—Only the brain examined. There was a recent posterior fossa decompression and burr holes for ventriculography were present in the parieto-occipital regions. The convolutional markings on the inner surface of the skull were pronounced. The floor of the sella turcica was membranous. The middle cranial fossæ and the lesser wings of the sphenoids on both sides were considerably eroded by pressure.



A B

FIG. 3.—*Case* 3. A. Hæmorrhagic infarction of the visual cortex. B. Necrosis and capillary hæmorrhages confined almost exclusively to the cortical grey matter. (Hæmatoxylin Van Gieson—low power.)

Both occipital lobes were very congested and soft in the inner and inferior surfaces. The condition was one of acute massive hæmorrhagic infarction (fig. 3A). On opening the lateral ventricles there was a bilateral hydrocephalus, and on removing the fornix a pale-green ball-like tumour was found attached slightly to the tela chorioidea and lying over the iter of Sylvius.

In the areæ parastriata and striata areas the cortex was somewhat soft and reddish brown in colour, this state being limited to the grey matter only and not extending into the subcortex. On the left side a small area of the posterior portion of the temporal lobe was similarly involved. The posterior cerebral artery, on macroscopical examination, appeared normal on both sides.

In the tegmental part of the pons extending up to the caudal third of the red nucleus there were multiple hæmorrhages in the distribution of the central arteries.

Histological examination.—The tumour was a colloid ball tumour (paraphysial cyst). The pontine hæmorrhages were composed of many small single hæmorrhages. The nerve-cells in the hæmorrhagic areas had undergone severe cell change. There was no glial or mesodermal reaction in the vicinity of the hæmorrhages. In the sections examined there was no evidence of rupture of the vessels. In a section from the right area parastriata the cortex showed multiple capillary hæmorrhages throughout its extent in two opposite gyri (fig. 3B). The nerve-cells in the affected area showed hyperchromatic nuclei and impregnation with formol pigment (hæmatin). The capillaries in the centres of the small hæmorrhages did not show endothelial cells with nuclei, but were represented by indistinct shadows of formol pigment, or showed an entirely amorphous structure. There was no glial or mesodermal reaction. The superficial layers showed much less hæmorrhage than the remaining part of the cortex.

The extracerebral arteries and veins of the area examined appeared normal.

Calcarine Infarction and Mid-brain Hæmorrhage.

Case 4.—A. C. (Case No. 109/35), male, aged 49 (Dr. George Riddoch), was admitted to hospital on December 12, 1935, complaining of continuous headache and frequent vomiting. One month before admission he had a sudden severe headache in the middle of the night which lasted fifteen minutes. It recurred the next night and the following day, and was then accompanied by vomiting. He also had tremor of the right hand and disturbance of taste. He lapsed into a deep coma on the day of admission. He vomited while comatose.

Examination.—The patient was deeply comatose and had stertorous respiration. The vomit contained coffee-ground material. The pulse-rate was 58. Both fundi showed papillœdema with retinal hæmorrhages. The swelling was four to five dioptres in each disc. There was bilateral ptosis. The corneal reflexes were absent. The left corner of the mouth was lower than the right. The remaining cranial nerves could not be tested properly. The limbs were flaccid and motionless, and the reflexes abolished. Sensation could not be tested.

On the day of admission an emergency ventricular tap was performed. The ventricular pressure was 330 mm. water pressure. The fluid from the left ventricle was clear and contained no cells, the total protein was 0·3 per cent. On the right side yellow fluid was obtained from a temporal cyst. The patient died the following day without having regained consciousness.

Post-mortem examination.—The skull was generally thin, especially both middle cranial fossæ, the right more than the left. The dura was very tense.

A soft cystic tumour occupied the inner part of the right temporal lobe, including the hippocampal gyrus and the uncus. The outer convolutions were quite flattened and very soft.

Multiple, diffuse hæmorrhages were present in the dorsal part of the mid-brain.

There was a hæmorrhage the size of an olive above the right lateral ventricle in the subcortical white matter of the superior portion of the caudal level of the parietal lobe. The walls of the hæmorrhagic cavity were smooth, and the clot was adherent only in a very small part.

The calcarine fissure and the adjacent areas of the cortex of the right occipital lobe were evenly shrunken and softened, and were of a greyish-brown colour with stippled reddish-brown areas. This change did not involve the subcortical white matter. The entire lesion extended from the parieto-occipital sulcus to the tip of the occipital pole. The left occipital lobe (macroscopically) was intact. The basilar and both posterial cerebral arteries showed no macroscopical changes.

Histological examination.—The tumour is a glioblastoma. In the right areæ striata and parastriata there are multiple capillary hæmorrhages throughout the grey matter. The capillaries show amorphous walls or have disintegrated. In some areas within the affected zone they are only extremely congested. The nerve cells in the same area show ischæmic and homogeneous cell change and are impregnated with formalin pigment (hæmatin). There is no glial or mesodermal reaction.

The extracerebral vessels are hyperæmic and show formalin pigment in fine dust-like granules in their wall.

The left occipital cortex shows a similar change but to a lesser degree.

Calcarine Softening.

Case 5.—C. P. (Case No. 72/33), female, aged 47 (Dr. F. M. R. Walshe), was admitted to hospital on September 26, 1933. She gave a history of headaches over a period of three years. There was trembling of the right hand eighteen months previous to admission, and an acute spastic paraplegia with loss of power of the legs thirteen months before entering hospital. The paraplegia lasted a fortnight, but cleared up completely. For several weeks before entering hospital she had severe headaches, numbness of the left side of the body, vomiting, loss of memory and failing vision.

Examination.—She manifested difficulty in understanding written words and her memory was very defective. There was a complete right homonymous hemianopia. The discs edges were blurred. There was numbness of the left side of the face. The tendon reflexes were more active on the right than on the left, and the right plantar response was in flexion whereas the left was in extension.

Lumbar puncture performed September 27 showed cerebrospinal fluid under a pressure of 275 mm. water, and containing a total protein of 0·175 per cent.

A right parietal decompression was performed October 10, 1933. The patient died on the following day.

Post-mortem examination.—There was a marked herniation of the uncus on the left side through the incisura tentorii, and a well marked notch was

present on the right crus at the junction of the pons and mid-brain. There was a well-marked cerebellar pressure cone. A firm tumour adherent to the dura was found in the region of the left marginal gyrus. There was an area of cortical softening affecting the territory supplied by the left posterior cerebral artery. This included the whole of the calcarine region and surrounding parts of the cortex (fig. 4).

The spinal cord was normal.

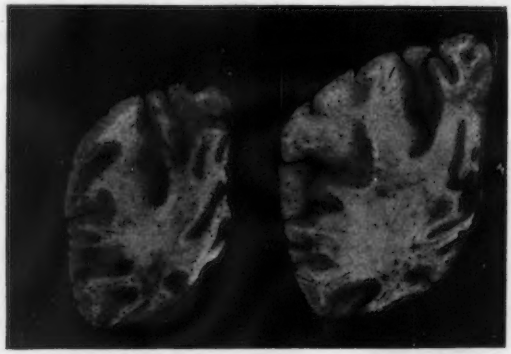


FIG. 4.—*Case* 5. Unilateral softening and shrinkage of the visual cortex.

Histological examination.—The tumour is an endothelioma. The affected cortical area shows a marked "gitter" cell formation in the lower cortical layers. The first two layers are better preserved. In Scharlach R preparations the gitter cells which are strictly confined to the grey substance contain bright red-staining substances.

The extracerebral vessels are normal.

Softening in Mid-brain.

Case 6.—W. G. (Case No. 48/37), male, aged 67 (Dr. Gordon Holmes), was admitted to hospital on April 5th, 1937, complaining of weakness, failure of memory, speech difficulty, drowsiness, restlessness and headaches. During February, 1937, the patient was taken ill with influenza, following which he remained quite weak, had persistent light-headedness, spoke in a silly fashion at times, had difficulty in reading and writing and developed headache and periodic attacks of drowsiness. The day before admission his drowsiness was interrupted by accesses of great violence and his speech was unintelligible.

Examination.—The patient was conscious, but was unable to give any information because of a severe dysphasia. He did not understand simple commands, and he was unable to write or name common objects. The discs were normal. There was disinclination to move the eyes to the right. The pupils were

irregular and the light response was diminished. There was some hypalgesia on the right half of the face. The right lower half of the face showed a marked weakness. The other cranial nerves could not be properly examined There was a mild right hemiparesis. The heart was moderately enlarged to the left. The blood-pressure was 170 systolic, 120 diastolic.

Lumbar puncture performed on April 12, 1937, showed the cerebrospinal fluid under a pressure of 300+ mm. water. The fluid was yellow, containing 25 cells, total protein 0·4 per cent., Nonne Appelt ++, Pandy +++, Lange and Wassermann negative. During the stay in hospital the patient deteriorated steadily. On April 13 an exploratory puncture of the left temporal lobe was made. The patient died on May 1, 1937.

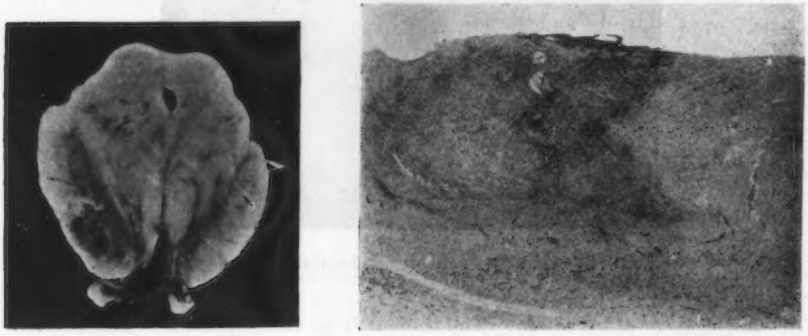


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Fig. 5.—*Case* 6. A. Softening in the mid-brain. B. Low power view of A. (Cresyl violet.)

Post-mortem examination.—Only the brain examined. The dura was moderately tense. There was no evidence of a cerebellar pressure cone. A brownish tumour mass was exposed filling the left optic thalamus and projecting into the 3rd ventricle. The tumour extended from the rostral end of the left thalamus to the posterior tip of the posterior horn of the lateral ventricle. It involved the basal ganglia and their surrounding structures and showed a partial gelatinous degeneration.

There was a greyish soft area in the mid-brain which extended from the medial 3rd of the peduncle along the substantia nigra up to the level of the oculo-motor nucleus (fig. 5A). The pons and the cortex of the occipital lobes appeared normal. The basilar artery and the posterior cerebral arteries were macroscopically normal.

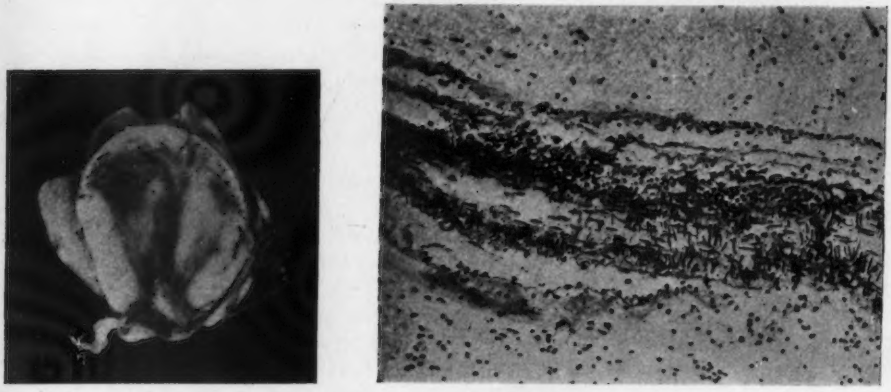
Histological examination.—The affected area in the pes pedunculi shows a softening in a rather early stage with an extensive glial reaction, formation of plump glial cells, capillary proliferation, but with few gitter cells yet developed

(fig. 5B). The ganglion cells of the substantia nigra are unaffected in the marginal zone of the area. The extracerebral vessels are normal.

Hæmorrhages in the Mid-brain and Pons.

Case 7.—L. J. (Case No. 31/37), male, aged 44 (Dr. C. P. Symonds), was admitted to hospital on March 23, 1937. His symptoms appeared in January, 1937, with convulsive seizures. Following this he progressively developed speech difficulty, drowsiness, emotional changes, and six days before admission a left homonymous hemianopia. The patient was left handed.

Examination.—Both optic discs showed blurred edges and the retinal veins were engorged. There was a divergent strabismus and the pupils were fixed



A B

FIG. 6.—*Case* 7. A. "Fountain-like" hæmorrhage in the mid-brain. B. Arteriole showing distension and partial dissection of the coats, subadventitial hæmorrhage, and marginal position and beginning emigration of the leukocytes.

to light. There was left facial weakness and left hemiparesis of the limbs with increased reflex activity.

On March 23, 1937, exploratory craniotomy revealed a right temporal lobe cyst. The patient died on the following day.

Post-mortem examination: There was no evidence of cerebellar or temporal lobe herniation. A soft brownish hæmorrhagic tumour mass involved the right temporal lobe, extending from the tip of the lobe well into the occipital lobe. A hæmorrhage, external to and below the posterior horn of the ventricle, formed the most backward portion of the mass. This hæmorrhage appeared

to be fresh. There were two hæmorrhagic areas in the mid-brain, one lying mesially near the caudal end of the red nucleus, the other being on the right side lateral to the central grey matter of the aqueduct. Both were surrounded by numerous punctate hæmorrhages. The tegmentum of the pons was also involved with numerous punctate hæmorrhages (fig. 6A). The basilar artery appeared normal.

Histological examination.—The tumour is a large-celled astrocytoma. The hæmorrhagic area in the mid-brain consists of many single hæmorrhages most of which show clearly their relationship to vessels. There are peri-adventitial hæmorrhages around arterioles extending into the surrounding tissue. The walls of the arterioles show all degrees of necrotic change. In some hæmorrhagic areas only the shadows of arterioles are to be seen in the centre. In some of these vessels the adventitia is to be seen in a disintegrating state and the hæmorrhage extending though the sub-adventitial into the peri-adventitial space. The leucocytes show a marginal arrangement in these vessels (fig. 6B). The capillaries are distended. The extracerebral vessels are dilated and full of blood, but apart from this are normal. There is no reaction of glial or mesodermal cells in the area of the hæmorrhage.

Hæmorrhages in the Mid-brain and Pons.

Case 8.—S. L. (Case No. 109/36), male, aged 45 (Dr. Gordon Holmes), admitted to hospital November 28, 1936. The patient contracted a septic infection of the left little finger in September, 1936, following which he developed convulsive seizures, headaches, vomiting, giddiness, forgetfulness, speech disorder, and visual disturbance.

Examination.—The following positive signs were found: general mental impairment, drowsiness, blurring of both optic discs and congestion of retinal veins, right corneal reflex sluggish, left lower facial weakness, weakness of left arm, abdominal reflexes absent bilaterally, extensor plantar reflex on the left side, slight loss of postural sense in left fingers and toes.

A transitory state of coma existed on the day after admission. During this coma the pulse was 70 and the blood-pressure 100 systolic, 70 diastolic. He regained consciousness, and on December 8, 1936, he again lapsed into coma and died the same day.

Post-mortem examination.—The dural sinuses were normal. There was a slight cerebellar pressure cone and a very marked herniation of both temporal lobes through the incisura tentorii, especially on the right side. On the right side, in addition, the anterior part of the lingual gyrus was purplish and showed small hæmorrhages. The right hemisphere was herniated under the falx cerebri.

There was a thin-walled abscess in the inferior portion of the right parietal lobe. The pons showed hæmorrhages in several areas, the largest being in the centre, and several small ones in the periphery (fig. 7). In the mid-brain there were many small hæmorrhagic areas at the level of the caudal end of

the red nucleus. Some of these were symmetrically situated between the red nuclei. The basal vessels appeared normal.

Histological examination.—A section (Nissl) from the area of the left herniated uncus shows a normal histological appearance of Ammons horn and the adjoining temporal gyri.

The pontine hæmorrhages show some tendency to spread in the direction of the surrounding myelin fibre network. These areas contain necrotic ganglion cells with marked incrustation of formalin pigment. There is no tissue reaction around the hæmorrhages. The extracerebral vessels appear normal.

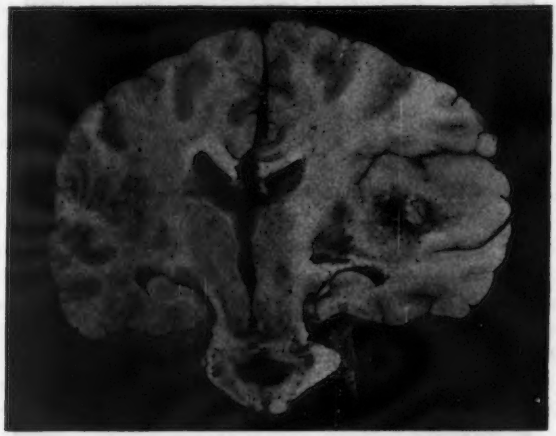


FIG. 7.—*Case* 8. Right parietal lobe abscess and central pontine hæmorrhage.

Pontine Hæmorrhage.

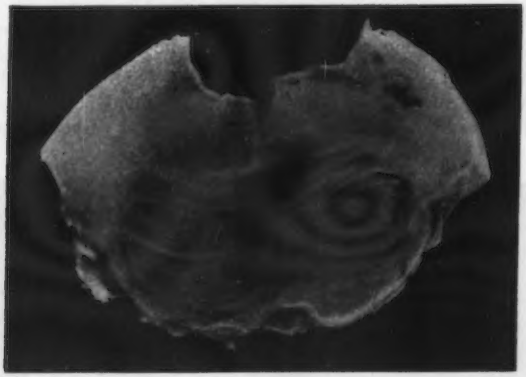
Case 9.—J. G. (Case No. 102/36), male, aged 58 (Dr. C. P. Symonds), was admitted to hospital on October 24, 1936. He had complained of frontal headache for one year and dizziness for six months preceding admission. There was a progressive deterioration in speech and strength for two months, and he began to have attacks of vomiting one month before coming to hospital.

Examination.—He showed a rather severe aphasia, a tendency to perseveration, and was unable to write despite being able to form letters. There was complete alexia. The edges of both discs were blurred and the retinal veins were full. Nystagmus was present, more marked on the right. There was a slight right lower facial weakness. The posture in the right arm was poorly maintained and he balanced insecurely on the right leg. The blood-pressure was 120 systolic, 85 diastolic.

Lumbar puncture on October 25, 1936, revealed a pressure of 165 mm.

water. The cerebrospinal fluid was slightly yellow and contained 14 cells to the cubic millimetre. The total protein was 0·22 per cent.

The patient died on November 12, 1936.



A

B

FIG. 8.—*Case* 9. Multiple pontine hæmorrhages at different levels (A, B).

Post-mortem examination.—The dura was very tense. There was no cerebellar pressure cone. The inner part of the left temporal lobe was herniated through the incisura tentorii. The crus on the right side was bruised fairly deeply and tore when the brain was turned over.

There was a tumour in the left middle temporal gyrus at the posterior end of the fissure of Sylvius. On section it extended inward and upward as a yellow degenerated mass.

The ventral part of the pons and most of the tegmentum (fig. 8A) was ploughed up by hæmorrhages. In the caudal 3rd of the pons the hæmorrhage appeared to be limited to the central core of the pons (fig. 8B).

The neighbourhood of the tip of the posterior horn of the right lateral ventricle was of a softened consistency. There was no evident disease of the blood-vessels.

Histological examination.—The tumour is a glioblastoma.

In a section from the pons (cresyl-violet), there are hæmorrhages in several layers, some of which show a small necrotic vessel in the centre. The ganglion cells in the hæmorrhagic area show severe cell change and are impregnated with formalin pigment. There is no mesodermal or glial reaction in the affected areas. The right cerebral cortex is normal histologically. The extracerebral vessels are normal.

Pontine Hæmorrhage.

Case 10.—F. H. (Case No. 74/36), female, aged 60 (Dr. G. Stewart), was admitted to hospital on August 18, 1936. She gave a history of convulsive seizures over a period of three years, weakness of the right leg, and later of the right arm, mental impairment and speech difficulty.

Examination.—She showed the following signs: A disturbance of speech comprehension, writing and memory; slight blurring and hyperæmia of the optic discs; right homonymous hemianopia, and right spastic hemiparesis.

A lumbar puncture performed on August 20, 1936, showed a pressure of 190 mm. water, clear, colourless cerebrospinal fluid, which contained no cells and a total protein of 0·09 per cent. The patient died on September 5, 1936.

Post-mortem examination.—There was a left frontal vertical endothelioma. The base of the sella was thinned, and the sphenoidal sinus contained some pus. The tumour lay immediately in front of the fissure of Rolando, sparing the paracentral lobule, and reaching half-way downwards to the Sylvian fissure.

There a was central hæmorrhage in the tegmental part of the pons which extended up to the level of the red nucleus. There were also small hæmorrhages in the peripheral areas of the pons. The rostral part of the central pontine hæmorrhage corresponded to the vascular distribution of the caudal twigs of the retromammillary (Foix-Hillemand) branches of the posterior cerebral arteries (figs. 9A, 9B, 9C). The basal vessels showed no changes macroscopically.

Histological examination.—The tumour is an endothelioma of very fibrous type. The section of the involved area shows a large hæmorrhage surrounded by a zone of vascular congestion. At another level not far distant from the main focus of hæmorrhage, the vessels are surrounded by a peri-adventitial hæmorrhage. The branches of the retromammillary vascular bundle are congested but show no mural change. At a level more caudal to the area of the hæmorrhage, the basilar artery shows intimal proliferation of a mild degree.

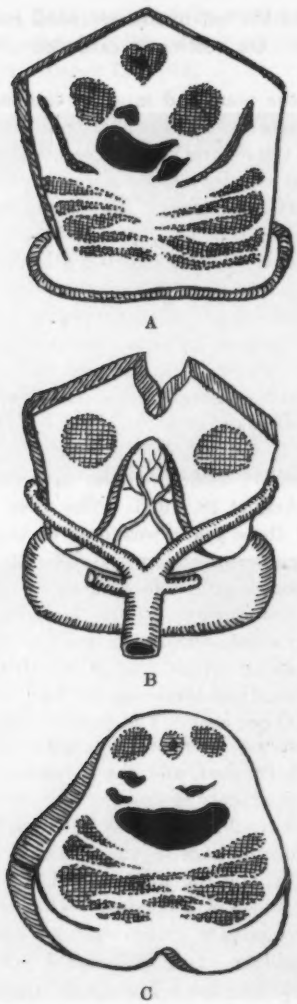


FIG. 9.—*Case* 10. Multiple central hæmorrhages in the mid-brain corresponding to the caudal branches of the retromammillary arterial bundle (B).

Hæmorrhages in Mid-brain and Pons.

Case 11.—C. C. (Case No. 98/35), female, aged 38 (Dr. F. M. R. Walshe), was admitted to hospital on October 31, 1935. There was a history of severe intermittent headaches since April, 1935, with periods of drowsiness and speech difficulties.

Examination.—There was a definite aphasia; blurring of both optic discs; right lower facial weakness, right hemiplegia; hypalgesia of the right side of the body; incontinence of urine. Lumbar puncture performed on November 9, 1935, showed a pressure of 300 mm. water. The cerebrospinal fluid was slightly yellow, contained 8 cells to the cubic millimetre, total protein 0·04 per cent. For twenty-four hours preceding death she was stuporous and the temperature was slightly elevated. She died on November 10, 1935.

Post-mortem examination.—The dura was tense and the convolutions were flattened in both hemispheres. There was no cerebellar pressure cone. A left temporal lobe tumour was found which extended into and involved the left frontal lobe, the 3rd ventricle, the right optic thalamus and the optic chiasma and optic nerves. The ventricular portion of the tumour was hæmo-

FIG. 10.—*Case* 11. Basal portion of the tumour, and pontine hæmorrhages from the central ascending branches of the basilar artery.

rrhagic. (Only the left half of the brain and brain-stem was available for examination.)

Several of the long central arteries of the pons and mid-brain showed peri-arterial hæmorrhages along their entire course (fig. 10). The substantia nigra showed greyish discoloration and engorged vessels. The basilar artery showed no pathological change.

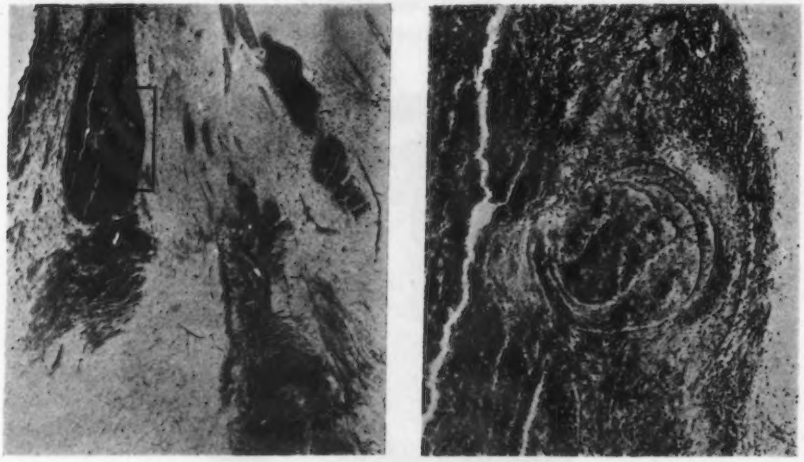
Histological examination.—The tumour is a glioblastoma.

A section at the rostral level of the left half of the mid-brain, shows peri-adventitial hæmorrhages around some of the central ascending arteries. The ganglion cells in this area are intact. There is no tissue reaction. The extracerebral vessels in the interpeduncular fossa are extremely dilated but otherwise normal.

Hæmorrhages in Mid-brain.

Case 12.—A. C. (Case No. 85/35), male, aged 55 (Dr. Gordon Holmes), was admitted to hospital in a comatose state on September 28, 1935. Headaches began gradually about one month before admission. There was a history of a convulsive seizure and of speech difficulties which began after the onset of headache. For a fortnight previous to admission the patient showed drowsiness alternating with restlessness, incontinence of urine, mumbling speech and finally coma. He had been a heavy drinker for many years.

Examination.—The patient was comatose and cyanotic, and had Cheyne-



A B

FIG. 11.—*Case* 12. A. Low power magnification showing the multiplicity of hæmorrhages and their arrangement around necrotic vessels. In the marginal zones the extravasated blood follows the network of the fibre-tracts. (Cresyl violet.) B. Complete splitting up and necrosis of the layers of the walls of a vessel within a hæmorrhage. Fig. 6B shows the same process in an early stage. (Cresyl violet—high power.)

Stokes' breathing. There was a blurring and hyperæmia of both optic discs, the pupils were equal in size, dilated and fixed to light, there was a spastic paralysis of the arms and legs, and bilateral plantar extensor responses. Lumbar puncture performed on September 28 showed a slightly blood-stained cerebrospinal fluid under a pressure of 5 mm. Three c.c. were removed and 30 c.c. of normal saline injected. The pulse became stronger, but soon thereafter weakened and the patient died.

Post-mortem examination.—The dura was tense and there was a slight cerebellar pressure cone. There was a definite herniation of the left uncus through the incisura tentorii. There was a tumour, hæmorrhagic on its under

surface in the left frontal pole. In the mid-brain there were multiple hæmorrhages from the central and peripheral vessels. The central hæmorrhages extended up to the level of the oculomotor nuclei. The hæmorrhages all appeared to be of the same age. The basal vessels appeared normal. The heart, aorta and kidneys showed no pathological changes.

Histological examination.—The tumour is a polar spongioblastoma.

A section of the brain-stem at the caudal level of the red nucleus shows multiple hæmorrhages in the area of the central ascending arteries. In each hæmorrhagic area a vessel, apparently the source of the hæmorrhage, is to be seen (fig. 11A). The vessel wall shows necrosis and the layers are partially split (fig. 11B). There is no glial reaction in the surrounding tissue. The ganglion cells in the involved areas have either entirely disappeared or show severe cell change. The extracerebral vessels in relation to the hæmorrhagic area are normal.

Hæmorrhages in the Mid-brain and Pons.

Case 13.—E. T. (Case No. 59/35), male, aged 47 (Dr. C. P. Symonds), was admitted to hospital on July 8, 1935. His symptoms began four months before admission, with focal convulsive seizures involving the right hand and face, weakness of the right arm and leg, and difficulty in speaking. These were followed within a month by loss of memory, drowsiness, loss of vision and increasing weakness of the right arm and leg.

Examination.—The patient showed speech disturbance and defect of memory. The optic discs were normal. There was a right hemiplegia. On the right side, sense of position, two-point discrimination, and vibration sense were greatly impaired.

Lumbar puncture performed July 9, 1935, showed a clear cerebrospinal fluid under 190 mm. water pressure, containing no cells, and a total protein of 0·075 per cent.

He had several convulsive seizures in hospital, and by July 18 had become quite drowsy. The edges of the optic discs were blurred and the right arm and leg had become spastic and powerless. He died on July 23, 1935.

Post-mortem examination.—The left parietal lobe bulged considerably and the convolutions in the upper part of the lobe were much widened and flattened. A cystic tumour, the size of a hen's egg, occupied the upper part of the parietal lobe. Very small nodules of tumour tissue were also found under the cortex of the right temporal lobe, near the vertex of the left frontal lobe, on the side of the mid-brain, and in the white matter of the cerebellum.

In the rostral part of the pons and the caudal part of the mid-brain there were multiple hæmorrhages, partly confluent, partly isolated, which seemed to be of the same age. The confluent hæmorrhages were from the central arteries. There was a small tumour nodule, the size of a pea, in the upper level of the ponto-cerebellar fibres and lying 2 mm. from the central hæmorrhage in the pons. The basal vessels showed no macroscopical abnormality.

Histological examination.—The tumour is a typical bronchial carcinoma of the oat-cell type.

The mid-brain hæmorrhages contain in their centre dilated vessels with amorphous walls. There is no tissue reaction round the hæmorrhage. The extracerebral vessels appear intact.

Hæmorrhages in the Mid-brain and Pons.

Case 14.—T. K. (Case No. 40/34), male, aged 49 (Dr. James Collier), was admitted to hospital on March 13, 1934. He gave a history of difficulty in reading for eighteen months preceding his admission. Weakness of the left arm and leg, and trouble with micturition began about two months before coming into hospital. He complained of headache when using his eyes for reading small print.

Examination.—The patient was drowsy and incontinent of fæces and urine. There was a left homonymous hemianopia. The optic discs were blurred and the retinal veins engorged. The pupils were irregular and inactive to light. There was bilateral ptosis of the lids, a marked left lower facial weakness, and a left spastic hemiparesis. All forms of sensation were impaired on the left side. Blood-pressure, systolic 105, diastolic 85. The patient died on March 19, 1934.

Post-mortem examination.—The dura was generally tense. The cerebral convolutions were flattened. There was a slight cerebellar pressure cone and the right uncus had herniated somewhat. There was an area of fluctuating swelling behind the Rolandic fissure and above the fissure of Sylvius on the right side. On incising here thin pus escaped. The cavity, about the size of a hen's egg, was thin walled.

In the upper third of the *pons* and at the level of the *posterior colliculi* there were small multiple hæmorrhages. Where the section was in the longitudinal direction of the vessels it could be seen that the hæmorrhage accompanied the vessel for some distance. The peripheral vessels were less affected than the central ones. The basal vessels appeared normal macroscopically.

There was a tumour in the region of the hilus of the lung.

Histological examination.—The tumour at the root of the lung is an oat-cell type of carcinoma.

The hæmorrhages in the pons contain necrotic ganglion cells with formalin pigment impregnation and dilated necrotic vessels which are situated in the centre of the hæmorrhagic area and are obviously the source of the hæmorrhage. There is no tissue reaction around the hæmorrhage. The right hippocampus and visual cortex are microscopically intact. The extracerebral vessels are normal.

Discussion.

Before discussing the merely pathological aspect and the pathogenesis of the lesions described, it would be well to consider first their clinical significance.

The calcarine softenings and the lesions in the brain-stem, whether softenings or hæmorrhages, are morphologically in no way distinguishable from those seen in cases of cerebral vascular disease. It is quite probable, therefore, that the clinical picture of these lesions is similar to that encountered in apoplectic seizures. There is, however, this important difference; in a case of brain tumour where a vascular lesion intervenes the latter affects a patient who usually has already shown neurological symptoms which may have come on suddenly with unconsciousness due to the growth of the tumour itself. If every apoplectiform manifestation in cases of brain tumour indicated that a vascular lesion had occurred locally and independent of the neoplasm itself, it might be expected that such pathological findings would be encountered more frequently than, in fact, they occur. On the other hand, in cases where the patient is bedridden, drowsy and shows poor co-operation, sudden events in the clinical course of the illness may escape detection.

In examining our case histories from this point of view, we find some in which the clinical equivalent to the vascular lesions described appears rather clearly.

In Case 3, the patient had suffered from severe headaches after a lumbar puncture, but in the succeeding three days he appeared quite well. Then one morning he could not be roused and the degree of coma made an emergency ventricular tap necessary. He died the same day. The gross and microscopic appearance of the involved tissues is typical of a fresh ischæmic infarction of the cortex and a fresh hæmorrhage into the brain-stem. They represent the anatomical equivalent of the sudden final event in the patient's history.

In Case 4, coma set in one day before death. Here fresh hæmorrhages without any signs of connective tissue or glial reaction were found in the mid-brain and occipital lobe, and it is very likely that the final comatose state was connected with these hæmorrhages. Cases 8, 11 and 12 are very similar, and they all showed a final comatose or stuporous stage. In view of the fact that in these cases the brain-stem hæmorrhage was fresh, we are inclined to regard it as the final cause of death and the anatomical equivalent of the final clinical picture.

It is quite evident that a localized cortical softening, not accompanied by a vascular lesion in the lower brain-stem, does not necessarily produce an alarming clinical picture. Thus in Case 5 the patient noticed a visual disturbance some weeks before admission, and on examination showed a right homonymous hemianopia. Corresponding to the clinical picture there was an ischæmic infarction of the left visual cortex which from

the histological appearance—shrinkage of the cortex and numerous gitter cell formation with marked fat inclusion—may have been several weeks old. Although not indicated by the clinical history, it is very probable that the visual disturbance came on suddenly as the result of the infarction of the visual cortex.

None of the cases showed focal symptoms which were suggestive of a pontine or mesencephalic lesion. In those cases in which the clinical picture gave any evidence at all of a lower brain-stem hæmorrhage the state of coma did not clear up sufficiently to permit an evaluation of pontine symptoms. This is all the more remarkable in that Bannwarth reports cases of cerebral tumours, complicated by brain-stem hæmorrhage, in which the diagnosis of a pontocerebellar angle tumour was made on the basis of the symptomatology.

From our experience we feel that when there is a sudden onset of profound unconsciousness, similar to certain apoplectiform pictures in other diseases, in a case of brain tumour it is suggestive of a complicating hæmorrhage in the lower brain-stem, even though this clinical picture also occurs in tumours without the complicating pontine hæmorrhage. Ponto-mesencephalic hæmorrhages always seem to be a fatal complication.

As regards the occipital lesions, the history in Case 5 shows that in cases of neoplasm in which a visual disturbance of cortical origin does not fit in with the remaining tumour symptomatology one must think of an occipital infarction which has no immediate local connection with the tumour itself.

The clinical history fails to give much information regarding the pathogenesis of the lesions under discussion. Surgical procedures *per se* can be excluded as a factor in their production. In ten of the fourteen cases reported no operative procedure had been carried out. Only in one case was there a time relation (Case 7); one day before death a craniotomy was performed and fresh pontine hæmorrhages were found on post-mortem examination. This may have been purely coincidental in this single case as such an association of events did not occur in the other cases. Therefore, we can state in accordance with Bannwarth and Rosenhagen that the vascular lesions described are not directly produced by cranial operations.

General vascular disease as a predisposing factor can be excluded. In Case 6, a single blood-pressure reading of 170 systolic, 120 diastolic was recorded. In another case (Case 10, female, aged 60) microscopical examination of the dissected basilar artery revealed an intimal pro-

liferation of the type found in early arteriosclerosis. The smaller local vessels showed no significant change. These two cases alone constitute those in which vascular pathology, of no great consequence, however, was found. It is safe to say, from what is known of the pathological work which has been done on the problem of apoplexy in arteriosclerosis, that a plaque in the basal main stem of the artery, such as appeared in Case 10, was not responsible for the type of hæmorrhage which occurred. All the remaining cases showed normal extracerebral arteries, and the intracerebral vessels exclusive of those situated immediately within the hæmorrhagic areas also were normal.

From the previous reports in the literature by Rosenhagen and Bannwarth it may be gathered that the increased intracranial pressure and cerebral œdema seem to play an important role in the production of the pontine lesions. Although the authors differ in their explanation of the pathogenesis of the pontine hæmorrhages they concur in emphasizing the above factor. The majority of our cases, in which cerebrospinal fluid pressures (ventricular and lumbar) were recorded, show evidence of increased intracranial pressure. One case (Case 12) showed an extremely low lumbar cerebrospinal fluid pressure, but in view of the cerebellar pressure cone found in this case no conclusion can be drawn concerning the state of the intracranial pressure.

Not only do the clinical reports suggest evidence of brain swelling and increased intracranial pressure, but the anatomical findings reveal these as well. Such signs as herniation of parts of the temporal lobe through the incisura tentorii, cerebellar pressure cone, and bone erosion were observed in eight of our reported cases.

Without considering at this time whether the described vascular lesions are produced by mechanical obstruction or by functional abnormalities of the vessels such as spasm or vasoparalysis, it may be said that the increased intracranial pressure acting as the sole factor cannot be the cause of the lesions. Were this so they would occur oftener than is the case. There must be something in addition which finally acts on the vessels to produce the changes seen.

A consideration of certain topographical conditions is necessary before elaborating further on this problem. The posterior cerebral arteries shortly after coming off from the basilar artery arch backward and upward between the crus cerebri and the uncinate convolution. During part of their course they may come in close to the free edge of the tentorium. An intracranial process which produces a herniation of the uncus through the incisura, would be likely to compress the posterior

cerebral artery so that the blood supply to the occipital lobe would be shut off. Thus a space-taking lesion above the tentorium might be sufficient to cause an obstruction of the posterior cerebral artery in this way. As has been shown by many observers, particularly those of the French school, Foix and Lévy (1927), Claude and Cuel (1927), and Ley (1931), a slowly developing obstruction to the arterial blood-flow may be compensated for, to an astonishing degree, by the anastomotic supply. This may be the reason for the infrequency of ischæmic lesions in the area supplied by the posterior cerebral artery. A slowly developing compression of the trunk of the artery would undoubtedly produce an organic change in the vessel wall and consequent thrombosis. Both from the fact that the occipital lesion is comparatively rare and that no organic changes of the vessel wall were found, we may conclude that the occipital lobe lesions were not the result of a gradual increase in intracranial pressure. We assume than an acute change in intracranial pressure relations, due either to an acute brain swelling or a sudden release of pressure in the subtentorial space, produces the train of events which lead to occipital lobe infarction. Even so, there is a question whether the merely mechanical occlusion of the artery by pressure from without is the actual cause of the infarction or whether repeated external mechanical irritation of the arterial wall produces a vasomotor disturbance. We cannot attempt an explanation of this question from our purely morphological investigation.

There is an essential morphological difference between the occipital and pontine lesions which have been described here. The occipital lobe lesion is a necrosis, confined to the grey matter only and may or may not be accompanied by capillary hæmorrhages. This is the typical ischæmic or hæmorrhagic infarction found in embolic or arteriosclerotic thrombotic lesions of the brain, i.e. it is typical of lesions produced by physical obstructions of arteries. These lesions, however, may also occur in arterial hypertension as shown by Neubürger (1930) and Hiller (1935).

The lesions in the brain-stem consist of multiple gross hæmorrhages. Their distribution is along the course of the arteries, arterioles or capillaries without any special predilection for the white or grey matter or anatomical structures, in contradistinction to the selective involvement of the cortical grey matter in the infarctions. This type of pontine lesion, as is known, is characteristic of the common apoplectic pontine hæmorrhage seen in arterial hypertension. To draw the analogy still closer, it was seen that the hæmorrhages tend to be related to the

long ascending central branches of the basilar artery, which also is typical of apoplectic lesions due to other causes (Foix and Hillemand (1925), Schwartz (1930), Stern (1933); furthermore, the histological appearance of the pontine lesions is identical with that seen in ordinary apoplexy. All the changes found in apoplexies of arterial hypertension, which were first described by Rosenblath (1918) and confirmed since then by Lindemann (1924), Westphal and Bär (1926), and Schwartz (1930), were found in our cases (figs. 6B, 9D, 11A and B), viz. the delamination of parts of the vessel wall, the marginal accumulation of leukocytes, the partial dissection of the layers of the vessel wall, and the acute "arterio-necrosis," all changes which occur suddenly and simultaneously in different arteries not related to each other. The striking similarity of the lesions described here with the pontine hæmorrhages found in hypertension permits of two deductions. First, that Rosenblath's hypothesis, of toxic (renal) genesis of the arterial and tissue necrosis (the latter being an assumption only) which precedes the hypertensive cerebral hæmorrhage is untenable. Secondly, it may be assumed from the morphological identity of the lesions that their pathogenesis has some common denominator.

From an analysis of our cases it seems probable that the arterio-necrosis is a secondary phenomenon, the result rather than the cause of the hæmorrhage, a point which already has been emphasized, in hypertensive and traumatic cerebral hæmorrhages, by Staemmler (1927). Where the hæmorrhage is not massive the vessel wall elements are clearly distinguishable, the layers being partially delaminated, the cell interstices extremely widened by a relaxation of all the coats of the wall (fig. 6B), bringing about a diapedesis or even rhexis. Only the vessels within the areas of massive hæmorrhage are necrotic, which observation lends support to the view that arterio-necrosis is produced secondarily by the hæmorrhage.

What does the similarity of the histopathological appearance of the lesions we have described with the hæmorrhages in arterial hypertension indicate? Concerning the latter much remains in the realm of pure conjecture as regards pathogenesis. It has been established that in hypertension the muscularis of the arteries is under abnormally high tension. If the similarities are carried over to our cases it would mean that the arteries of the pons and mid-brain likewise were under a high tension, or, at any rate, that the mechanism which finally leads to the hæmorrhage is essentially the same in both arterial hypertension and cerebral tumours.

Animal experiments have shown that a sudden rise in the intracranial pressure which retards the blood circulation within the cranial cavity by compression of the vessels is regularly followed by an increase of the systemic blood-pressure (Wolff and Forbes (1928); Wolff and Blumgart (1929)). The systemic blood-pressure rises until the abnormal resistance in the intracranial vessels is overcome. This reaction can only be obtained by a sudden increase of the intracranial pressure, not by a slow gradual increase. Otherwise we should expect to find a constant arterial hypertension in most cases of cerebral tumour.

As the histological picture of the arteries in our case is identical with the acute changes found in association with the hæmorrhages in arterial hypertension, we abandon Bannwarth's view of an arterial hæmorrhage by mere congestion. It is much more likely that the same mechanism—rise of the systemic blood-pressure following a sudden rise of the intracranial pressure—applies here. Such a transient rise of the systemic blood-pressure may easily escape clinical observation.

If this be so, why are the hæmorrhages confined to the pontine branches of the basilar artery? There are several factors which produce a *locus minoris resistentiæ* in these arteries. We are in accord with Bannwarth's view that the effect of the intracranial pressure must be more marked near the outlet of the cranial cavity, i.e. foramen magnum.

Kolisko emphasized that the basilar artery lying fixed for a long distance parallel to a bony surface is more exposed to the increased intracranial pressure than the other basal arteries. This view, put forward to explain post-traumatic hæmorrhages, was adopted by Rosenhagen to explain the pontine hæmorrhages in brain tumours.

It is true that after the compression of an artery which produces ischæmia, the release of pressure may produce hæmorrhages in the terminal branches of this artery, as is known from the arteries of the extremities. Such hæmorrhages are petechial; one could so explain the petechial hæmorrhages in the neighbourhood of the iter and the 4th ventricle following trauma (Duret's hæmorrhages). The pontine hæmorrhages as we have seen them, however, are arterial, and, moreover, the complete absence of infratentorial tumours in our material and in that of Rosenhagen and Bannwarth indicates that the effect of compression of the basilar artery is insignificant.

It is generally known from the uncinate herniations and the notching of the peduncle that the increase of supratentorial pressure exerts its main effect on the rostral end and bifurcation of the basilar artery.

We explained thus the compression of the posterior cerebral artery. The softening in Case 6 (fig. 5) which was localized in the peduncle on the side opposite to the side of the tumour is presumably caused by the immediate compression of an arteriole. The same mechanism, however, may cause an arterial congestion of the basilar artery and make this area predisposed to the final hæmorrhage.

Thus, besides reflex rise of the systemic blood-pressure we have to consider a local predisposing factor, i.e. the congestion of the basilar artery by the partial obstruction in the area of its outflow. It still remains undecided why in one case the posterior cerebral artery and in another the basilar artery is more affected. It is probable that minute individual differences in the topography of this area account for the different behaviour.

Summary and Conclusions.

Vascular lesions in the brain-stem and calcarine cortex occurring in cases of space-taking lesion of the brain and in no immediate juxtaposition to the tumour itself have been studied in eighteen cases.

Fourteen cases are described clinically and pathologically. In five there was involvement of one or both occipital lobes, combined or not with lesions of the brain-stem. In the remaining cases only brain-stem lesions were found.

With the exception of one case (softening in the peduncular region), the brain-stem lesions consist of multiple fresh hæmorrhages from arteries. Histologically they resemble hæmorrhages in arterial hypertension. The occipital lesions are hæmorrhagic or ischæmic infarctions.

It is suggested that sudden changes in the pressure relationship between the supra- and infratentorial spaces lead to disturbance of the circulation in the area of the rostral end of the basilar artery. Compression of the posterior cerebral artery causes occipital infarction. Arterial congestion in the basilar artery causes a predisposition to hæmorrhages which are finally brought on by reflex rise of the systemic blood-pressure.

Surgical procedures seem to have no pathogenetic significance.

The clinical picture of the brain-stem hæmorrhages is that of a sudden onset of unconsciousness. They seem to be fatal in every case.

The occipital lesions have their clinical counterpart in apoplectiform manifestations or visual disturbances which complicate the neurological picture.

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OBSERVATIONS ON THE PATHWAYS TRANSMITTING THE SENSATION OF TASTE.

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INTRODUCTION.

LUSSANA (1869, 1871-72), on the basis of clinical and experimental observations, described a pathway for the transmission of gustatory sensation from the anterior two-thirds of the tongue. According to his description (fig. 1), which is now generally accepted, the impulses

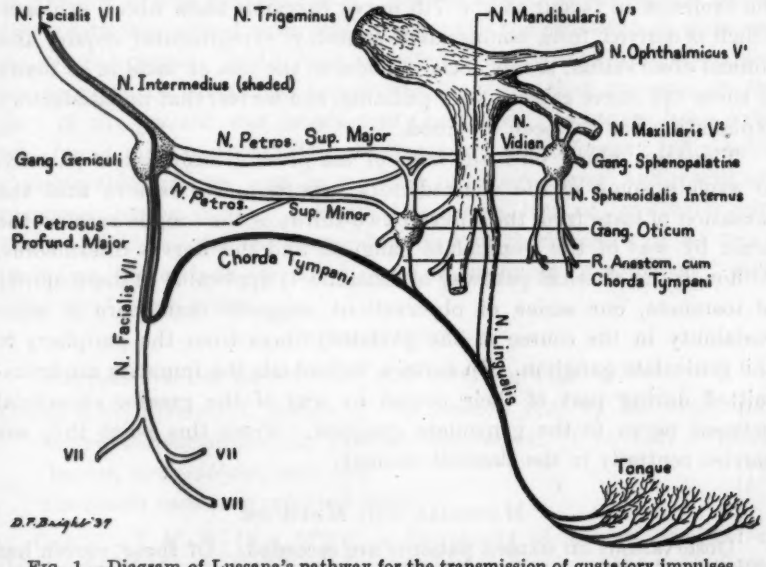

FIG. 1.—Diagram of Lussana's pathway for the transmission of gustatory impulses from the anterior two-thirds of the tongue.

are carried by the chorda tympani, which joins the facial nerve *en route* to the geniculate ganglion; from this point fibres reach the brain-stem through the sensory portion of the 7th nerve (pars intermedia, or nervus intermedius of Wrisberg).

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It is not the purpose of this report to present a review of the literature on the subject. This has been exceedingly well done by Cushing (1903) and Lewis and Dandy (1930). Cushing presented evidence in favour of Lussana's path, and Lewis and Dandy in a series of classical experiments upon humans came to the same conclusion. Subsequently Reichert and Poth (1933) and Reichert (1934) added confirmatory evidence.

Although the foregoing observations appear to be conclusive, no attempt has been made to reconcile the conflicting opinions scattered through the literature. Gowers (1880-82, 1893, 1902) and Schiff (1870, 1887, 1896) insisted that taste was mediated through the 5th nerve; Oppenheim (1911) and Harris (1926) concluded that the pathway may vary in different individuals. Recently, Carmichael and Woollard (1933), in a critical study of the 5th and 7th cranial nerves stated: "Though the evidence in favour of the 7th nerve carrying taste fibres, evidence which is derived from comparative anatomy, experimental inquiry and clinical observation, seems decisive enough, the loss of taste in so many of these 5th nerve cases is very puzzling, and we feel that no satisfactory explanation has yet been obtained."

The cases which form the basis of the present communication seem to explain some of the contradictory reports. We believe that the sensation of taste from the anterior two-thirds of the tongue reaches the brain by way of the geniculate ganglion and the nervus intermedius. Although the classical pathway of Lussana is applicable in the majority of instances, our series of observations suggests that there is some variability in the course of the gustatory fibres from the periphery to the geniculate ganglion. In certain individuals the impulses are transmitted during part of their course by way of the greater superficial petrosal nerve to the geniculate ganglion. From this point they are carried centrally in the classical manner.

Material and Methods.

Observations on sixteen patients are recorded. Of these, eleven had had trigeminal sensory root section by the temporal approach for relief of tic douloureux. In five patients radical mastoidectomy was performed. The cases were chosen from a group at Barnes Hospital within a three-month period. Except where otherwise noted, all special examinations were made by us and demonstrated to the neurosurgical staff.

The necessity of controlling the means of testing taste has been emphasized (Lewis and Dandy, 1930). Care must be taken to exclude

diffusion of substances, olfactory influences, and guessing on the part of the patient. Three standard crystalline substances—cane sugar, sodium chloride and quinine sulphate—were used. The subject's tongue was protruded and the tip was held lightly with gauze by the examiner. Crystals of the test substance were moistened with tap water and applied to specific areas of the tongue. The use of moist crystals assured maximum concentration, and spread was more easily controlled. Because of difficulty in accurately controlling diffusion of acid or "sour" solutions, these categories of taste were omitted. After the test substance was applied to the protruded tongue, the patient was asked to point to the name of the taste experienced, a printed list of various tastes being held before the patient. Time of response was measured; no result was considered negative until sixty seconds had elapsed following application of the moist crystals. Between applications of substances, the mouth was rinsed with tepid water until the sensation of taste was no longer present. In all cases repeated examinations were made, and the sequence of substances tested was varied so that guessing on the part of the patient was satisfactorily excluded. As others have done, we found some variability of response in different individuals. Considerable patience may be required to obtain honest and intelligent responses, owing in large measure to patients' lack of familiarity with the test. Using the technique described in thirty cases of all types, including the sixteen presented here, no instances of so-called "taste blindness" were found.

Observations.

The material has been divided into several groups:—

Group I.—Differential section of the sensory root of the trigeminal nerve uncomplicated, i.e. without involvement of petrosal or facial nerves, and without taste loss.

Four such cases are reported here:—

Case 1.—I. M. B. (No. 57768), a 59-year-old white man, admitted on October 24, 1936, with a history of tic douloureux involving the right second division. Pre-operative neurological examination was negative. Special examinations of 5th and 7th nerves revealed no abnormality. No subjective taste disturbance. Tests of gustatory function produced normal, prompt responses for sweet, salt and bitter over both sides of tongue, front and back. On October 27, 1936, Dr. Ernest Sachs performed a differential section of the sensory root on the right side. The dura was easily stripped up from the temporal fossa, and the sensory root was exposed without difficulty. The petrosal nerves were not seen.

Post-operative course was uneventful. There was no facial paralysis. There was anæsthesia over all three divisions of the right trigeminal nerve, involving all forms of sensation, except recognition of large deformities of the skin. Deep pressure pain was increased from 0·25 kg. (pre-operative) to 2·0 kg. over all three divisions. No subjective taste disturbance. Taste was tested on October 30, 1936, with the following results.

	Right	Left
Anterior 2/3		
Sweet[1]	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt
Posterior 1/3		
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

[1] In this and subsequent records of taste performance, "prompt" indicates the response given two to three seconds after application of the test substance.

Case 2.—M. E. T. (No. 58352), a 54-year-old white woman, admitted on November 29, 1936, with a history of tic douloureux involving the second division on the left side. The patient had hypertension with arteriosclerotic heart disease. Neurological examination revealed no abnormalities except for slightly less acute corneal reflex on the left than on the right. Otherwise the 5th nerve was normal. No facial weakness. No subjective or objective taste disturbance.

On November 30, 1936, Dr. Sachs performed a differential section of the left sensory root. The petrosal nerves were not seen.

Post-operative course was uneventful. There was anæsthesia over the third division, including the left half of the tongue. There was hyperæsthesia over the second division. The first division was essentially spared. Corneal reflex on the left was slightly less active than on the right, as before operation. No facial weakness. No subjective taste disturbance. Taste was tested on December 8, 1936:—

	Right	Left
Anterior 2/3		
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt
Posterior 1/3		
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

The patient returned for a visit on December 28, 1936, and again on April 2, 1937. She was completely free of pain. Sensory loss as noted above; no taste disturbance.

Case 3.—N. E. F. (No. 59148), a 53-year-old white woman, admitted on January 18, 1937, with a history of tic douloureux of twelve years' duration.

Originally confined to the third division, pain subsequently spread to the first and second divisions, on the right side. There was a definite trigger zone inside the right lower lip. The only abnormality revealed on examination consisted of slight weakness of the right pterygoids. This was considered to be due to multiple peripheral alcohol injections which had been made earlier without relief. No sensory changes over domain of trigeminal nerve. Facial nerve intact. No subjective taste disturbance. Pre-operative tests revealed the following :—

	Anterior 2/3	
	Right	Left
Sweet	20 sec.	10 sec.
Salt	15 sec.	Prompt
Bitter	10 sec.	10 sec.

The posterior part of the tongue could not be tested due to the patient's inability to open her mouth sufficiently widely.

Differential sensory root section on the right on January 19, 1937. The procedure was uncomplicated. Dr. Sachs noted that the middle meningeal artery was absent. Petrosal nerves were not exposed in the field, nor was the sulcus n. petrosi superficialis majoris of the temporal bone seen.

The post-operative course was uneventful. No facial weakness. There was complete anæsthesia over the third division, including the right half of the tongue and hyperæsthesia over the first and second divisions. Deep pressure pain was increased from 0·5 kilograms (preoperative) to 1·0 to 2·0 kg. after operation. No subjective taste disturbance. Taste was tested on January 23, 1937, with the following results :—

	Anterior 2/3	
	Right	Left
Sweet	7 sec.	7 sec.
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

Case 4.—B. L. H. (No. 59180), a 35-year-old white woman, admitted on January 19, 1937, with history of tic douloureux involving the second division on the left side. Neurological examination, including special examinations of 5th and 7th nerves, was negative. No subjective taste disturbance. This patient was not tested by us before operation, but the routine neurological examination is recorded as showing " taste normal and equal on both sides."

On January 20, 1937, differential section of left sensory root was performed by Dr. Sachs. The dura in this case was very friable and was opened without complete stripping from the floor of the temporal fossa. The petrosal nerves were not exposed or damaged.

Post-operative course was uneventful. No facial weakness. There was anæsthesia of the third and hypæsthesia of the second divisions. Sensation was intact over the first division. The right side of the tongue was anæsthetic. No subjective taste disturbance. Taste was tested on January 24, 1937, with the following results :—

			Anterior 2/3	
			Right	Left
Sweet	..	..	10 sec.	7 sec.
Salt	..	..	Prompt	Prompt
Bitter	..	..	Prompt	Prompt
			Posterior 1/3	
Sweet	..	..	5 secs.	Prompt
Salt	..	..	5 secs.	Prompt
Bitter	..	..	Prompt	Prompt

Comment.—The observations on the patients in this group confirm the fact that taste is not transmitted by the second or third divisions of the trigeminal nerve. It has been proved conclusively (Lewis and Dandy, 1930) that gustatory impulses are not carried by any portion of the sensory root. These cases are included in the present study to demonstrate that there was no interference with the petrosal nerves nor any apparent injury to the geniculate ganglion.

Group II.—Differential Section of Sensory Root followed by Disturbance of Taste on the Homolateral Side.

This group embraces several categories.

A.—Sensory Root Section with Facial Paralysis and Taste Loss.

No attempt will be made to give the individual records of at least four available instances in which facial paralysis appeared after operation for trigeminal section, accompanied by loss of taste over the homolateral anterior two-thirds of the tongue. These cases were operated upon before we became aware of the importance of the greater superficial petrosal nerve. Accordingly there is insufficient data upon which to form any unorthodox opinion. The only thing that can be said is that the operative procedures in these four cases were complicated by technical difficulties. In view of the occurrence of facial paralysis in these four cases, it is conceivable that the hemigeusia may have resulted from injury to the geniculate ganglion by force transmitted through the petrosal nerves. Such a mechanism was postulated by Dixon (1897) and Lewis and Dandy (1930).

Besides the category just alluded to, however, we have found several patients, with post-operative gustatory loss, observations on whom are significant.

B.—Differential Section with Injury to Greater Superficial Petrosal Nerve, Facial Paralysis and Taste Loss.

Case 1.—C. A. W. (No. 57621), a 57-year-old white woman, admitted on October 15, 1936, with a history of tic douloureux involving the second and third divisions on the right side. There was a trigger zone inside the right lower lip. Neurological examination, including special examination of the 5th

and 7th nerves revealed no abnormality. No subjective taste disturbance. Pre-operative taste examination showed prompt responses for all substances on both sides.

On October 17, 1936, Dr. Sachs performed a differential section of the right sensory root. During the operation it was necessary to cut several bands in the region of the petrosal nerves, because of dural adhesions. This was done deliberately with the hope of preventing facial paresis due to traction.

Post-operatively there was almost complete lower facial paralysis on the right side. There was anæsthesia over the second and third divisions of the trigeminal nerve, with hypæsthesia of the first division. No subjective taste disturbance. Taste was tested on October 22, 1936 :—

		Anterior 2/3	
		Right	Left
Sweet	.. ..	Absent	Prompt
Salt	.. ..	Absent	Prompt
Bitter	.. ..	Absent	Prompt
		Posterior 1/3	
Sweet	.. ..	Prompt	Prompt
Salt	.. ..	Prompt	Prompt
Bitter	.. ..	Prompt	Prompt

The patient returned on December 21, 1936. Exactly the same findings were present; there was no evidence of return of facial nerve function. On March 17, 1937, there was some slight recovery of facial function; sense of taste was still absent on the right anterior two-thirds of the tongue.

Case 2.—M W. M. (No. 57860), a 76-year-old white woman, was admitted on October 29, 1936, with a history of tic douloureux of five years' duration. All three divisions on the left side were affected. There was a trigger zone inside the left nostril. General physical examination showed hypertensive heart disease. The only abnormal neurological finding consisted of absent corneal reflex on both sides, although both corneæ were sensitive. The facial nerve was intact. No subjective or objective taste disturbances.

On November 3, 1936, Dr. Sachs performed a differential section of the left sensory root. The operation was complicated by extremely friable dura and unusual bleeding from dural and periosteal vessels. There was a great deal of trauma to the superficial petrosal nerves.

Post-operatively there was anæsthesia over the second and third divisions, except for preservation of sensation of very light touch (cotton wisps) and normal deep pressure pain. There was slight facial weakness on the left side. Taste was tested on November 15, 1936 :—

		Anterior 2/3	
		Right	Left
Sweet	.. ..	Prompt	Absent
Salt	.. ..	Prompt	Absent
Bitter	.. ..	Prompt	Absent
		Posterior 1/3	
Sweet	.. ..	Prompt	Prompt
Salt	.. ..	Prompt	Prompt
Bitter	.. ..	Prompt	Prompt

On December 13, 1936, the patient returned for re-examination. Facial paresis had improved markedly; only the slightest weakness of the left orbicularis oculi remained. Tests of gustatory function at this time showed exactly the same findings as those recorded above.

Comment.—In these two cases there was damage to the superficial petrosal nerves, and indirect injury to the facial. The resultant loss of taste on the homolateral anterior two-thirds of the tongue can, of course, be explained (as the cases in sub-group A) on the basis of a geniculate ganglion lesion, and it might be reasonably postulated that petrosal nerve trauma was not the primary factor involved. However, the possible importance of the petrosal nerves cannot be dismissed entirely, even though the mass of evidence is preponderantly against their playing a direct rôle.

C.—Sensory Root Section with Section of Greater Superficial Petrosal Nerve, without Peripheral Facial Paralysis, and with Taste Loss.

The patient, A. A. McN. (No. 59153), a 50-year-old white woman, was admitted on January 18, 1937, with a history of tic douloureux involving the second division on the right side of three years' duration. Neurological examination was negative. There was slight facial asymmetry due to partial adentia; there was a suggestion of slight central facial weakness on the right. Special examinations revealed no abnormality of the 5th nerve. No subjective taste disturbance. Pre-operative taste test revealed somewhat sluggish responses on both sides over the anterior two-thirds of the tongue. Sluggishness of response was thought to be possibly associated with foul breath; the patient had almost given up the use of a toothbrush because of pain.

	Anterior 2/3	
	Right	Left
Sweet	10 sec.	10 sec.
Salt	8 sec.	10 sec.
Bitter	5 sec.	5 sec.

The posterior one-third of the tongue could not be tested because of pain.

On January 19, 1937, Dr. Leonard T. Furlow performed differential section of the right sensory root. The dura was easily stripped back and intentionally dissected farther posteriorly than usual to expose the sulcus n. petrosi superficialis. The petrosal nerves were clearly visible in the depths of the sulcus. Without further dissection and without traction a segment of the greater superficial petrosal nerve was excised (microscopic sections subsequently showed this segment to consist of numerous large myelinated fibres). Following this procedure, dissection of the dura was resumed anteriorly and the operation was then carried out in the usual manner.

Post-operative course was uneventful. There was complete anæsthesia of the third division, including the right half of the tongue, and hypæsthesia of

the first and second divisions. No facial weakness. No subjective taste disturbance. Taste was tested on January 24, 1937 :—

	Anterior 2/3	
	Right	Left
Sweet	Absent	10 sec.
Salt	Absent	10 sec.
Bitter	Absent	Prompt

The patient returned for re-examination on February 21, 1937, and May 1, 1937. General condition excellent, patient entirely free of pain. Sensory loss as before. No facial weakness or subjective taste disturbance. Gustatory function :—

	Anterior 2/3	
	Right	Left
Sweet	Absent	Prompt
Salt	Absent	Prompt
Bitter	Absent	Prompt

Comment.—This record we regard as especially significant. Th greater superficial petrosal nerve was deliberately cut, in a relatively easy operative procedure, without any trauma to the geniculate ganglion. Although prior to operation there was thought to be slight central facial weakness, there was no pre-operative taste loss. Following operation, central facial weakness was no longer evident ; there was no sign of peripheral facial weakness, but there was hemigeusia over the anterior two-thirds of the tongue. It may be concluded that in this case taste was transmitted, for part of its course, by the greater superfical petrosal nerve.

Group III.—Radical Mastoidectomy with Facial Paralysis and with Loss of Taste.

The chorda tympani, after entering the tympanum through the aperture of the canaliculus chordae, courses anteriorly on the upper part of the tympanic membrane in the notch formed by the crus of the incus medially, and the anterior process of the malleus laterally ; it then passes above the tensor tympani muscle to the petro-tympanic fissure. It is apparent, therefore, that the chorda tympani cannot escape if the tympanic ossicles are removed.

In the cases of this and the following group, radical mastoid operations, with complete removal of the ossicles, were performed by Drs. M. F. Arbuckle and A. C. Stutsman. We wish to express our gratitude to them for permission to use this material, which represents not a carefully selected group, but simply five patients who happened to be available in the hospital at about the same time.

Case 1.—P. D. W. (No. 58867), a 27-year-old white school teacher, was admitted on January 4, 1937, complaining of chronic discharge from the right ear for eighteen years. During exacerbations of the disease the patient noticed taste deficiency on the right side of her tongue.

On January 4, 1937, right radical mastoidectomy with removal of the ossicles was done. Post-operatively, neurological examination was negative. Special tests revealed no abnormality of the 5th or 7th cranial nerves. Taste was tested on January 8, 12 and 17, 1937 :—

	Anterior 2/3	
	Right	Left
Sweet	Absent	Prompt
Salt	Absent	Prompt
Bitter	Absent	Prompt
	Posterior 1/3	
Sweet	Prompt	Prompt
Salt..	Prompt	Prompt
Bitter	Prompt	Prompt

Case 2.—O. R. K. (No. 59196), a 24-year-old white man, was admitted on January 19, 1937, with a history of chronic discharge from the right ear of four years' duration. No subjective taste disturbance.

On January 20, 1937, right radical mastoidectomy, with removal of the ossicles and a portion of the tympanic membrane, was performed. Post-operatively, neurological examination was negative, including special tests of the 5th and 7th cranial nerves. Taste was tested on January 25, 1937 :—

	Anterior 2/3	
	Right	Left
Sweet	Absent	30 sec.
Salt	Absent	20 sec.
Bitter	Absent	Prompt

Case 3.—W. R. S. (No. 56500), a 49-year-old white man, was admitted to the nose and throat service of Barnes Hospital on November 4, 1936. He had been admitted previously on August 17, 1936, complaining of chronic discharge from both ears. A simple mastoidectomy had been performed on August 18, 1936. This was followed by sinus thrombosis, requiring secondary incision with drainage of the lateral sinus and ligation of the left jugular vein. On the second admission, the patient showed signs of lung abscess, in addition to the persistent left aural discharge. On December 1, 1936, thoracostomy with drainage of a large empyema cavity was performed by Dr. Brian Blades. The patient recovered from this procedure to permit a left radical mastoidectomy on January 9, 1937. Post-operative course was smooth. Examination showed no abnormal neurological findings, except for taste.

Taste was tested on January 22, 1937, and again on February 7, 1937 :—

	Anterior 2/3	
	Right	Left
Sweet	Prompt	Absent
Salt..	Prompt	Absent
Bitter	Prompt	Absent

Comment.—These cases represent pure lesions of the chorda tympani and demonstrate the dependence of the sensation of taste on this nerve.

Group IV.—Radical Mastoidectomy without Facial Paralysis and without Loss of Taste.

Case 1.—M. L. J. (No. 58919), a 57-year-old white woman, was admitted on January 5, 1937. There was a history of chronic discharge from the right ear following acute otitis media, seven years previously. She had never noticed any difficulty in tasting; indeed, her sense of taste, developed through years of preparing highly-seasoned German dishes, was known to be extraordinarily acute. Olfactory sense, however, was poor due to frequent obstruction of the nasal passages by mucous.

Right radical mastoidectomy on January 6, 1937. The facial canal was exposed. Auditory ossicles were found in the remaining fragment of the drum and were removed. Post-operatively there was no abnormality of the 5th or 7th nerves; no subjective taste disturbance. Taste was tested on January 9, 1937. The responses were phenomenally rapid, answers being given immediately on touching the tongue with the test material.

			Anterior 2/3	
			Right	Left
Sweet	..	..	Instantaneous	Instantaneous
Salt..	..	..	Instantaneous	Instantaneous
Bitter	..	..	Instantaneous	Instantaneous
			Posterior 1/3	
Sweet	..	..	Instantaneous	Instantaneous
Salt..	..	..	Instantaneous	Instantaneous
Bitter	..	..	Not tested	Not tested

The examination was repeated on January 11, 1937:—

			Anterior 2/3	
			Right	Left
Sweet	..	..	Instantaneous	Instantaneous
Salt..	..	..	Instantaneous	Instantaneous
Bitter	..	..	Instantaneous	Instantaneous

Case 2.—C. E. T. (No. 58484), a 24-year-old white woman, was admitted on December 6, 1936, with a history of discharge from the right ear of three months' duration. Nine years previously the patient had acute otitis media, which was treated by incision of the drum. Following that episode there were intermittent periods during which she was troubled with discharge from the affected ear. No subjective taste disturbance.

On December 7, 1936, right radical mastoidectomy was performed. The middle ear and antrum were filled with granulation tissue; the ossicles had been partially absorbed. The mass was removed, including a small persistent remnant of the drum anteriorly. Post-operatively, the 5th and 7th nerves were normal. There was no subjective taste disturbance.

On January 12, 1937, taste was tested:—

	Right	Left
Anterior 2/3		
Sweet	Prompt	Prompt
Salt..	Prompt	Prompt
Bitter	Absent	Prompt
Posterior 1/3		
Sweet	Absent	45 sec.
Salt..	Prompt	Prompt
Bitter	Prompt	Prompt

It should be noted that although salt was equally and promptly recognized on both sides of the anterior two-thirds of the tongue, the patient stated that the sensation was not quite as distinct on the right as on the left. Sweet was tasted equally distinctly on both sides. On January 30, 1937, the patient was re-examined. All substances were recognized promptly and equally, and there was no subjective difference:—

	Right	Left
Anterior 2/3		
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt
Posterior 1/3		
Sweet	Prompt	Prompt
Salt	Prompt	Prompt
Bitter	Prompt	Prompt

Comment.—In these two cases, the chorda tympani was cut near its point of union with the facial nerve. Schiff (1870) contended that, in animals, section of the chorda tympani at this point is not invariably followed by taste loss. However, since Blau's (1879) accurate observations on a patient with a fistula of the middle ear, there has been no suggestion that taste is not carried by the chorda tympani. In the recent literature, Reichert and Poth reported four cases in whom the chorda tympani had been cut in the course of radical mastoidectomy; each of these showed hemigeusia on the homolateral anterior two-thirds of the tongue.

We are aware, therefore, that the preservation of taste in two of our cases is a most unusual and unexpected finding. It should be emphasized that, although the incidence is two out of five patients included in this report, we believe that the percentage is probably much smaller, and that the appearance of these two cases has been merely fortuitous. It must be concluded, however, that, in at least these two cases, the impulses of taste are carried, for at least part of their course, by a pathway which does not involve the proximal segment of the chorda tympani.

Summary of Cases Presented.

Group I.—Differential Section of the Sensory Root, uncomplicated.

Four cases are noted, in which sensory root section was done, without interference with the petrosal nerves or injury to the geniculate ganglion. Taste was preserved, thus showing that gustatory impulses are not transmitted by the second or third divisions of the trigeminal nerve.

Group II.—Differential Section followed by Homolateral Taste Disturbance.

A. Four instances in which facial paralysis appeared post-operatively, accompanied by taste loss over the anterior two-thirds of the tongue. Because of operative trauma, the results may be said to have depended upon possible injury to the geniculate ganglion by force transmitted through the petrosal nerves.

B. Two cases, with known injury to the petrosal nerves and indirect trauma to the facial nerve. In these there was hemigeusia.

C. One case, with deliberate excision of a portion of the greater superficial petrosal nerve, without trauma to the facial nerve, and with loss of taste over the homolateral anterior two-thirds of the tongue.

Group III.—Radical Mastoidectomy without Facial Paralysis and with Taste Loss.

Three cases in which the chorda tympani was excised during the course of radical mastoidectomy, followed by preservation of facial innervation, with loss of taste over the homolateral anterior two-thirds of the tongue.

Group IV.—Radical Mastoidectomy without Facial Paralysis and with Preservation of Taste.

There are two cases in this group, in which taste was preserved although the chorda tympani was excised during radical mastoidectomy.

Discussion.

From the observations on the single patient in Group II *C*, it must be concluded that the greater superficial petrosal nerve may at times transmit the sensation of taste. The question immediately arises concerning the complete pathway involved. Schiff (1870, 1887, 1896) had suggested that taste impulses were carried to the geniculate ganglion by

the chorda tympani; transmission then occurred from the ganglion by way of the greater superficial petrosal nerve to the sphenopalatine ganglion; thence by way of the second division of the 5th nerve to the gasserian ganglion, and finally through the sensory root to the central nucleus. On the basis of our own observations and the reports in the literature, we do not believe that the 5th nerve is in any way involved with the transmission of taste.

There is adequate anatomical and embryological (Dixon, 1897; Hunt, 1937; Larsell and Fenton, 1928; Yagita, 1914) evidence that the greater superficial petrosal nerve forms, with the chorda tympani, the most important portion of the sensory system of the 7th nerve, arising from cells of origin in the geniculate ganglion; the small superficial and both deep petrosal nerves are not a part of the geniculate system. This evidence in itself would serve to invalidate Schiff's theory. It is reasonable to assume that sensory impulses which reach the greater superficial petrosal nerve must be conveyed centralwards to the geniculate ganglion.

The exact mechanism by which gustatory impulses reach the greater superficial petrosal nerve remains unsolved. During the course of his experiments Schiff (1870) found that, in some cases, section of the lingual nerve above its point of union with the chorda tympani was followed by partial loss of taste; also, as noted previously, he observed that section of the proximal segment of the chorda tympani did not always result in taste loss. Accordingly he considered that not all the taste fibres passed through the chorda tympani, but that part passed through the lingual. In offering an alternative pathway, therefore, he postulated that taste may be carried through the lingual to the otic ganglion, by way of an inconstant branch. From this point, he stated the impulse might be carried to the geniculate ganglion by the small superficial petrosal nerve, and finally away from the ganglion by way of the great superficial petrosal. Morphological evidence, previously offered, does not permit ascribing such functions to the petrosal nerves. Although it is improbable, we must admit the possibility that impulses may pass from the lingual, by an inconstant branch, to the otic ganglion. This connection is so inconstant (Hyrtl, 1866), however, as to render such a course doubtful.

If the participation of the lingual nerve be dismissed, it would be justifiable to assume some connection from the chorda tympani which would serve as a shunt. The cases in Group IV demonstrate that, in some instances, section of the chorda tympani in the middle ear is not

followed by hemigeusia. It follows, therefore, that a communication must be given off by the chorda tympani, distal to the tympanum and proximal to its point of union with the lingual nerve. According to Quain (1895), Poirier and Charpy (1901) and Rauber (1909) there is a communication which leaves the chorda tympani, just above its junction with the lingual, and joins the otic ganglion. From the otic ganglion, these same anatomists describe the internal sphenoidal nerve which connects with the vidian nerve. At the point where the large superficial and deep petrosal nerves unite to form the vidian, Quain and

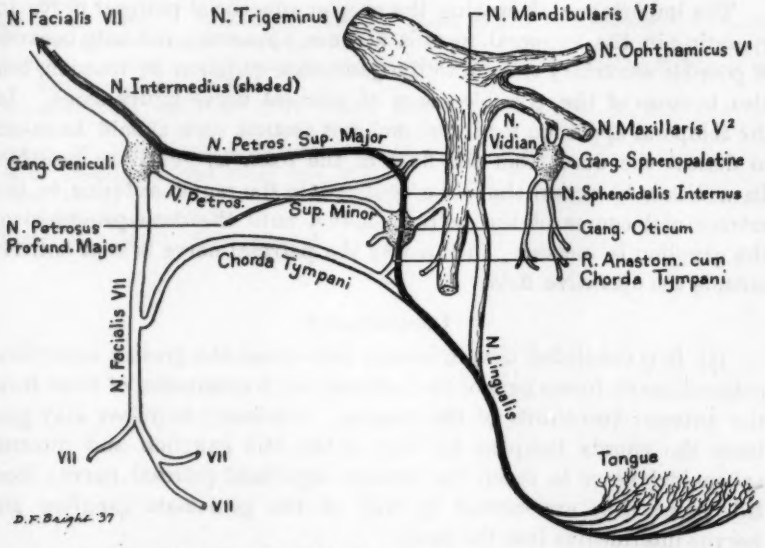

FIG. 2.—Suggested pathway for taste transmission from the anterior two-thirds of the tongue in a limited number of cases.

Rauber illustrate a bifurcation of the internal sphenoidal nerve, with one limb in intimate relation with the greater superficial petrosal nerve.

Until further evidence is obtained, a pathway for taste sensation, other than the usual course first advocated by Lussana, may be postulated as follows. The impulse is transmitted by the chorda tympani to the otic ganglion; from there, by way of the internal sphenoidal nerve, to the greater superficial petrosal nerve; thence to the geniculate ganglion and nervus intermedius, to the brain-stem (fig. 2). This is the probable course of taste fibres in a small percentage

of cases; but we believe that in the majority of instances the classical pathway of Lussana is correct.

The implication of the greater superficial petrosal nerve in the mechanism of taste transmission may serve to explain some of the apparent discrepancies in the literature. It is not at all improbable that operative interference with, or alcohol injection of, the gasserian ganglion, involves secondary damage to the petrosal nerve. This may account for some of the cases of taste loss in trigeminal lesions reported, among others, by Gowers (1880-82, 1893), Harris (1926), Carmichael and Woollard (1933).

The importance of sparing the greater superficial petrosal nerve in operating in the temporal fossa is at once apparent; not only because of possible secondary trauma to the geniculate ganglion by traction, but also because of the possible effect of petrosal nerve injury alone. In the temporal approach for trigeminal root section, care should be taken to dissect the dura from the floor of the fossa as gently as possible. In addition dissection should be confined to the region anterior to the intracranial course of the petrosal nerve, until the dura propria over the ganglion is incised. In this way the petrosal nerve is kept entirely outside the operative field.

Conclusions.

(1) It is concluded that in certain individuals the greater superficial petrosal nerve forms part of the pathway for transmission of taste from the anterior two-thirds of the tongue. Gustatory impulses may pass from the chorda tympani by way of the otic ganglion and internal sphenoidal nerve to reach the greater superficial petrosal nerve; from this point they are carried by way of the geniculate ganglion and nervus intermedius into the pons.

This conclusion is based chiefly upon the following observations: (*a*) Loss of taste in one patient following excision of the greater superficial petrosal nerve; (*b*) preservation of taste in two cases following section of the chorda tympani.

(2) Additional cases are presented in which taste impulses follow the classical course, by way of the chorda tympani directly to the geniculate ganglion and nervus intermedius.

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A CASE OF PRIMARY GENERALIZED AMYLOID DISEASE WITH INVOLVEMENT OF THE NERVES.

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So-called primary generalized amyloid disease unassociated with antecedent infection is now well recognized, and several clinical and pathological types have been described. Of the clinical forms, the combination of unexplained cardiac failure, peripheral neuritis, and diarrhœa forms the salient feature in the majority of reported cases. In the present case this association of symptoms first suggested the tentative diagnosis of beri-beri.

We have been unable to find any reference in the accounts of published cases to amyloid disease involving the nerves. Where the signs and symptoms of peripheral neuritis have been present they have been attributed to the amyloid infiltration affecting the peripheral blood-vessels.

Two reasons have prompted us to publish our findings on this case. In the first place, the pathological examination of the nervous system shows that in generalized amyloid disease infiltration may occur in the peripheral nerves, as well as in the heart and elsewhere. Secondly, its similarity, both clinically and pathologically, to other cases of primary amyloid disease, and in particular to a case of hypertrophic polyneuritis described by De Bruyn and Stern (1929)[1], may serve to draw attention to this occasional involvement of the nervous tissue by amyloid infiltration as a possible explanation of the peripheral neuritis which may accompany this uncommon though well-defined disease.

[1] Through the kindness and interest of Dr. J. G. Greenfield, one of us (S.DeN.) has been able to examine and compare the posterior root and sympathetic ganglia and peripheral nerves from De Bruyn and Stern's case, and there can be little doubt that the "plasmatic bodies" which they described are nodular deposits of amyloid. This is confirmed by the severe infiltration which is present in the arteries and perineurium. Unfortunately, it is impossible to employ special stains for amyloid, owing to the age of the material. The histological appearance of the ganglia and nerves in sections stained with hæmotoxylin and eosin and Van Gieson's method are so strikingly similar to our case that it leaves little room for doubt.

Case Report.

Christopher A., aged 36, was admitted to Guy's Hospital complaining of diarrhœa, dizziness on exertion and gross muscular wasting and weakness.

His father had died at a great age, and his mother was alive and well. He had eleven siblings, one of whom was killed in the war; the rest were well. No other member of his family had ever suffered from symptoms resembling his own. He had married eleven years previously and had a daughter, aged 9, born at seven months. Another premature child died aged 2 months. There were no miscarriages and his wife was healthy. He denied any venereal infection.

He was apprenticed as an engineer in boyhood and had been in this occupation ever since. At no time had he worked with lead or in circumstances where any of his colleagues acquired any industrial disease.

Until four years before his admission he had had a healthy athletic life. At this time he had become an engineer's foreman, and no longer had time for his athletics. Up to this time he had never been ill or seen a physician. In the autumn of that year he had developed a series of minor carbuncles on his left forearm and face, none of which had been severe enough to leave more than a small pitted scar. These carbuncles had persisted for some weeks, and had been followed by an occasional septic spot ever since. None of these was present during his admission.

Two years previous to admission he had developed a nocturnal diarrhœa, passing about five loose motions in the night, but none by day. He began to feel physically weak and became impotent. About this time he developed bilateral hydroceles which slowly increased to a considerable size. Gradually he became weaker, his muscles wasted, and he became increasingly short of breath and dizzy on exertion. On one or two occasions after short brisk exertion he had become momentarily unconscious.

A year before admission he was seen at Guy's Hospital Out-patients, and was found to have a hæmoglobin of 58 per cent. He was treated for this anæmia with large doses of Blaud's pill without symptomatic improvement. His diarrhœa now occurred by day and night, and urgency of defæcation developed. The stools were very loose, but not otherwise abnormal. At this time he developed difficulty of micturition, passing a very small stream with much effort. He was compelled to give up his work on account of his weakness and shortness of breath.

His appetite remained good throughout the duration of his illness, and he continued his habit of eating a generous diet, including plenty of fresh fruit, meat and vegetables. His alcohol and tobacco consumption was very moderate.

During the course of his illness he developed numerous telangiectases about his face and neck, which bled on the slightest trauma, and at times he bruised with extreme ease.

On examination at time of admission he was 5 ft. 9 in. in height, and

8 stone 10 lb. in weight. There was gross wasting of the voluntary muscles, but his subcutaneous fat was normal. His skin generally, but especially where it had been exposed to light, was of an olive green colour, accentuated by contrast with the telangiectases and ecchymoses about his face and neck. This colour was not jaundice, his sclerotics being of normal hue. There were no local thickenings or cutaneous deposits. Neither fingers nor toes were clubbed.

Cardiovascular system: He had a regular pulse of 70 to 90. The blood-pressure was 135/100. A soft systolic murmur was heard over the whole præcordium, and gallop rhythm was present on all occasions. There was slight œdema in the lumbar region and over the tibiæ, but no abnormal filling of the veins of the neck was seen. Measured orthodiagraphically, the transverse diameter of his chest was 26 cm. and of his heart 15·3 cm. There was a uniform enlargement of all its chambers. Numerous X-rays taken during

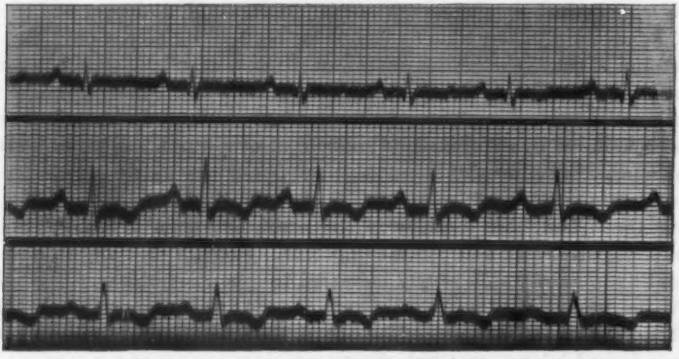

FIG. 1.—Electrocardiogram showing some inversion of T.2 and T.3.

his eight weeks' stay in hospital revealed little change in its size and shape. An electrocardiogram taken soon after admission showed some inversion of T.2 and T.3 (fig.1). This inversion became slightly less on later occasions.

Respiratory system: No abnormality was detected.

Alimentary system: His tongue was very smooth and clean, the edges showing almost complete atrophy of the filiform papillæ. It was pale, but neither swollen nor sore. His abdomen was normal. Nothing abnormal was detected on rectal examination. His liver, spleen and kidneys were not palpable.

Genito-urinary system: Bilateral hydroceles of considerable size were present. His testes and penis were unusually large, but otherwise normal.

His urine (sp. gr. 1010 to 1018) was neutral and constantly contained a good trace of albumin. Occasionally he passed some bright blood with the urine, either mixed with it, or at the end of micturition. No sugar was found on any occasion.

Central nervous system: His personality was cheerful, and he was at all times co-operative. His intelligence was above the average. The optic discs appeared normal.

His pupils were small, regular and central, but did not react to light and only sluggishly on convergence. There was no ptosis. He occasionally had some photophobia. His other cranial nerves showed no abnormality.

The muscles of both limbs and trunk were grossly wasted and proportionately weak, so that on admission he was unable to walk, and had difficulty in turning about in bed. His arm-jerks were present but very feeble, and his knee and ankle jerks were absent.

No abnormalities of the senses of touch, pin-prick, heat, cold, vibration, position or movement were demonstrated.

Muscular co-ordination was good so far as weakness allowed of its investigation. His muscles and tendons were not abnormally tender, though he complained of occasional cramp-like pains at night. The peripheral nerves were not unusually palpable, and the external popliteal and ulnar nerves especially felt of normal size.

Other organs: There was no enlargement of the lymph-glands nor signs of abnormality of the glands of internal secretion.

Laboratory findings: Test meal—achylia, some delay in emptying. Bile present in all specimens.

Fæces examination: Slightly alkaline, no excess of fats, no meat fibres or starch granules. Occult blood tests consistently negative, except on one occasion following epistaxis.

Alimentary X-ray: Stomach and duodenum, normal in all respects. In one hour, head of meal in jejunum; in three hours meal already reached cæcum and colon; in five hours a trace in the stomach, bulk in the cæum and rectum; appendix canalized and apparently normal, colon normal; in twenty-four hours, all evacuated.

Cerebrospinal fluid: Pressure 90 mm. no block, fell to 0 after 5 c.c. were removed. Fluid; clear, 6 red cells, and 1 lymphocyte per cmm. Protein, 160 mgm. per cent. (Mestrezat's Method). Pandy test, positive. Lange curve 2443333200. Wassermann and Kahn reactions, negative both in blood and cerebrospinal fluid.

Blood: Hæmoglobin 82 per cent; red corpuscles 4·1 million; reticulocytes 4·5 per cent.; white cells 12,900; polymorphs 70·5 per cent.; eosinophils 3·5 per cent.; basophils 2 seen in 600 cells; lymphocytes 24 per cent.; hyalines 2 per cent. Platelets 80,000, rising to 130,000 in four days, when they remained approximately constant. Clotting time, seventy seconds; bleeding time, three minutes twenty seconds.

Serum proteins: 5·35 per cent. (albumin 3·65 per cent.; globulin, 1·69 per cent.) Blood chlorides, 0·68 per cent. No abnormal capillary fragility by the venous compression test.

H. M. Sinclair, of Oxford, kindly estimated the apparent concentration of vitamin B_1 in the blood and found it to be within normal limits.

Urine: Ascorbic acid output, 3·0 mg. *per diem.*

During the eight weeks between his admission and his death, his diarrhœa was rather intermittent, and during the periods of the watery diarrhœa he became very exhausted. At no time was pus or blood seen in the stools, nor did he have any colic. His œdema varied, but it was never gross. He had no enlargement of the liver or congestion of the veins of his neck till terminally.

He was put on a light residue-free diet and his appetite remained good.

A tentative diagnosis was made of beri-beri, due to failure to absorb vitamin B_1 owing to a chronic enteritis. He was therefore treated by daily intravenous injections of 100 mg. of pure synthetic crystalline vitamin B_1.[1] Though he stated that this reduced his weakness, no improvement was demonstrable objectively. His heart remained of the same size, and, apart from some slight improvement in the electrocardiogram, there was little change in his condition.

He suffered from a mild influenzal attack in the fourth week of his stay, from which he recovered rapidly. But in the seventh week he developed a sore throat, during a ward epidemic, and hæmolytic streptococci were found in swabs from his tonsils. His diarrhœa became rapidly worse, leading to incontinence. More marked signs of cardiac failure appeared. Finally, he became rapidly more dyspnœic and cyanosed and died in about an hour from the onset of these more severe cardiac manifestations. Apart from these two infections he was apyrexial.

Autopsy Findings.

P.M. No. 118/37. The autopsy was performed twenty-four hours after death, the body having been kept in a refrigerated mortuary. The body was of medium build, showing wasting of the muscles and little subcutaneous fat. There was no œdema of the legs, but some over the lumbar region. There were numerous petechiæ on the limbs and trunk.

Cardiovascular system.—The pericardial sac was normal. The heart weighed 750 grm. and was considerably enlarged on both sides. The myocardium was uniformly pale, double the normal thickness, firmer than normal in consistency and showed loss of muscular texture. The columnæ carneæ and papillary muscles were hypertrophied. The chambers were dilated and contained a little post-mortem clot. Apart from slight atheroma of the aortic cusp of the mitral valve, which extended to the aortic ring, there was no endocardial or valvular abnormality. The coronary arteries were normal. The aorta showed a little superficial fatty atheroma in streaks and was smaller than normal for the man's size, both in the diameter of its lumen and the thickness of its wall. The pulmonary artery and venæ cavæ were normal.

Respiratory system: The pleural cavities each contained 250 c.c. of slightly blood-stained fluid. There were a few sub-pleural petechiæ at the left base.

[1] Kindly supplied through Professor Peters, of Oxford, by Messrs. Bayer and Messrs. Hoffmann-La Roche.

The lungs were moderately emphysematous but partially compressed, though air-containing throughout. The right and left lungs weighed 775 and 700 grm. respectively.

Alimentary system: The stomach was greatly distended with gas and bile-stained fluid, but the mucous membrane appeared normal. The first metre or so of jejunum was distended, and beyond that point some 30 cm. of jejunum were hæmorrhagic, with thickened œdematous walls and dark-red necrotic mucous membrane. This portion was infarcted. The intestinal tract beyond this point was of normal diameter, though the walls were thickened and firm in consistency. The mucous membrane showed numerous hæmatomata, varying in size, from a few mm. to 1 cm. in diameter. These were particularly numerous in the pelvic colon. The peritoneal cavity contained 2 litres of blood-stained cloudy fluid, which in the pelvis was purulent. The peritoneum throughout showed a fibrino-purulent exudate of recent origin which was hæmorrhagic in the region of the infarcted jejunum. The liver weighed 1,650 grm. and was slightly enlarged, pale and firm in consistency. Gall-bladder, biliary tracts and pancreas normal.

Lymphatic system: The spleen weighed 250 grm., was twice the normal size with smooth surface and uniformly pale, but with firm pulp in which the Malpighian follicles were obscured.

Urinary system: The kidneys each weighed 125 grm. and were normal in size, pale with finely scarred surfaces and moderately adherent capsules. The cortices showed slight contraction and irregularity at the periphery, but the rest of the parenchyma was normal. The pelvis of the right ureter showed a large submucous hæmorrhage. The bladder was normal except for submucous petechias in the region of the trigone. Bilateral hydroceles each containing 100 c.c. of clear fluid were present. The prostate was normal and the testes were uniformly enlarged.

Endocrine system: the right and left suprarenal glands weighed 15 and 10 grm. respectively. (Normal weights=8 to 10 grm.) The pattern was normal. The thyroid was normal.

Nervous system: The meninges, brain, and spinal cord appeared normal, but all the posterior root ganglia were enlarged to approximately double the normal size. The right ulnar, peroneal and sciatic nerves were similarly enlarged throughout their courses and firmer than normal in consistency.

Iodine test: It was not until the tissues were examined histologically that amyloid disease was discovered and the test was done on the heart, liver, spleen, and kidneys, which had been fixed in formalin. The test was slightly positive in the heart, spleen and kidneys, but negative in the liver. In the heart the characteristic dark brown colour was noticeable in the epicardium and in the sub-endocardial tissue, while in the kidney it was confined to the medulla.

Histological Examination.

General remarks: Sections were taken of the heart, voluntary muscle, lungs, intestines, liver, pancreas, spleen, abdominal lymph-glands, kidneys,

thyroid, suprarenal glands, testes, brain, spinal cord, posterior root ganglia and peripheral nerves. The following stains were employed: hæmatoxylin and eosin, Van Gieson's and Weigert's stains for fibrous and elastic tissues respectively, methyl violet, methyl green, and Congo red for amyloid, Marchi's method for nerve tissue, and osmic acid for fat.

With hæmatoxylin and eosin the amyloid was represented as a homogeneous substance, bright pink in colour, of glassy appearance and devoid of structure. When freshly stained, methyl violet, methyl green and Congo red confirmed the presence of amyloid, though methyl green was the most successful of the special stains. The amyloid was present in all the tissues examined with the exception of the brain and spinal cord.

Heart: The auricles were more severely affected than the ventricles, and this was probably due to the relatively greater amount of connective tissue in the former. Both the auricles showed numerous nodular deposits, fairly uniform in size, in the epicardial and sub-endocardial tissues and in the vicinity of the vessels in the myocardium. In addition, all the small arterioles and arteries showed more or less complete replacement of the media and adventitia by amyloid. The muscle fibres were considerably atrophied and showed loss of striation and pyknosis and kariolysis in the nuclei. There appeared to be more amyloid than parenchyma and connective tissue combined. In the ventricles the amyloid was evenly distributed through the inter-fascicular connective tissue, epicardium, and sub-endocardium and the walls of the smaller arteries and arterioles. The muscle cells were markedly atrophic.

Voluntary muscles: Sections were taken from the pectoral and calf regions and showed only slight infiltration of the arterioles and perivascular connective tissues with amyloid.

Nervous system: The brain and spinal cord were unaffected with the exception of the choroid plexus, which showed a perivascular infiltration of amyloid, particularly around the arterioles and capillaries. The dura of the cord, however, showed an occasional minute deposit of amyloid. The posterior root and sympathetic ganglia from the cervical, thoracic and lumbar regions, but particularly the last, showed severe amyloid disease. The fatty connective tissue which surrounds the ganglia showed a delicate reticulum of amyloid lying between and accentuating the outlines of the fat cells, while numerous small deposits were present in the walls of the arteries. The most striking change was inside the ganglia, which contained numerous nodules scattered diffusely in the interstices between the ganglion cells and axis cylinders. The ganglion cells were surrounded by masses of amyloid (fig. 2). Their cytoplasm was coarsely granular and vacuolated and their outline was indented and irregular. Many of the ganglion cells were diminished in size, and appeared compressed by the amyloid, while the course of the axis cylinders was distorted. The ulnar, sciatic, and peroneal nerves were similarly affected. The connective tissue sheaths of the nerve bundles and particularly the perineurium were irregularly thickened by numerous oval or rounded nodular deposits (fig. 3), while individual nerve fibrils appeared compressed and deviated by similar

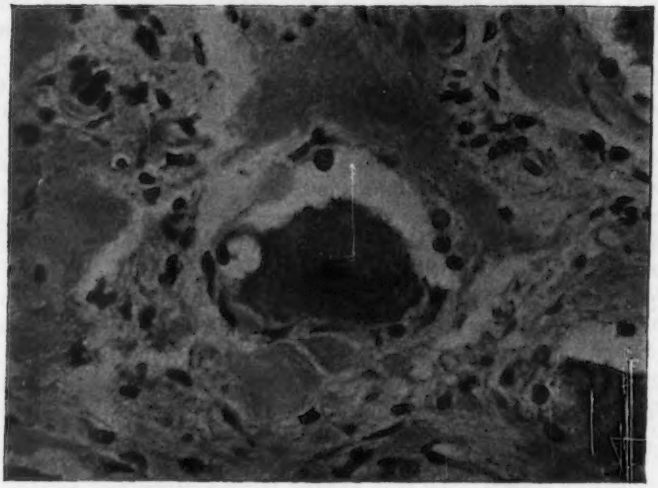

FIG. 2.—Photomicrograph of posterior root ganglion showing atrophy of a ganglion cell which is surrounded by amyloid. H. and E. × 410.

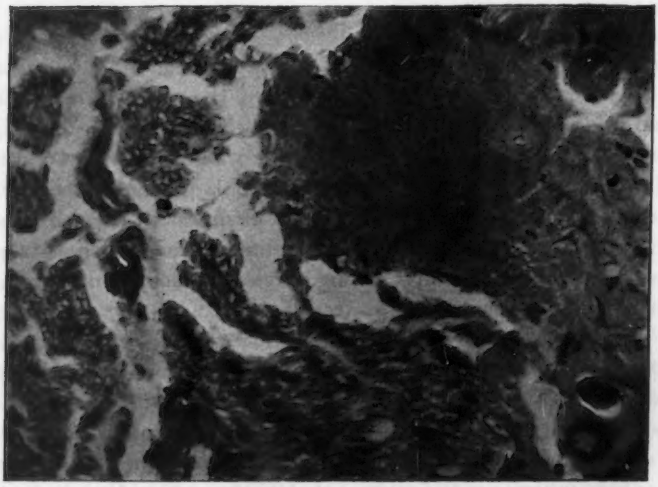

FIG. 3.—Photomicrograph of sciatic nerve showing amyloid infiltration of the connective tissue. H. and E. × 340.

deposits. In addition there was a diffuse delicate infiltration of the connective tissue of the nerve by amyloid deposits, which radiated from the arteries, whose media and adventitia were uniformly infiltrated.

Alimentary system: The small and large intestine showed diffuse amyloid deposits in the submucosa, which extended into the intestinal villi and caused them to become distended and separated from one another, and from the underlying muscle. The arteries and the veins showed severe medial deposits of amyloid, which extended into the connective tissue of the mesentery. No occlusion of the mesenteric vessels was found to account for the infarction of the loop of jejunum, but the amyloid infiltration of the arteries and veins was particularly severe in this region.

Hepatic system: The liver was scantily affected: the amyloid was confined to the small hepatic arteries and the connective tissue of the portal areas. The parenchyma was normal.

Lymphatic system: The spleen showed a diffuse amyloid infiltration of the trabeculæ and small arteries, but no nodular deposits like those present in "sago spleen" were present. The mesenteric lymph-glands showed amyloid infiltration of the capsules and peripheral sinuses only.

Respiratory system: The lung showed minute deposits of amyloid in the arterioles and in the bronchial muscle only.

Endocrine system: The thyroid, suprarenal glands and testes showed both diffuse and nodular deposits of amyloid throughout the vessels and connective tissue, which had caused considerable compression and atrophy of the parenchyma, particularly in the testes, where spermatogenesis was absent.

Commentary.

Cardiac failure.—In the absence of hyperplastic or hyaline arteriolar changes indicative of hypertension, and in the presence of extensive amyloid infiltration of the heart muscle, the great increase in weight of the heart is referable to the bulk of amyloid. This is well supported by the clinical picture in which symmetrical enlargement of both sides of the heart, the gallop rhythm, the E.C.G. changes, all pointed to a pure muscular failure. The cause of this failure appears to be atrophy of the muscle fibres due to surrounding amyloid rather than to ischæmia, from narrowing of the coronary arterioles.

Alimentary system.—Though, as in most reported cases, diarrhœa is an outstanding gastro-intestinal symptom, constipation has been reported in a few. The diarrhœa is associated in this case with intestinal hurry and not with any derangement of digestion or absorption of fat.

Muscular System.—In contrast to the cardiac muscle, the weakness of voluntary muscles is to be attributed to changes in the nerves. The pectoral and gastrocnemius muscles were free from amyloid, though

clinically weak and wasted. Unlike the case described by Parkes-Weber and others (1937), there was no evidence of arterial obstruction, clinically or pathologically.

Nervous system.—The difficulty in micturition, impotence, and pupillary changes, can be explained by the infiltration of the autonomic nervous system.

Abstracts of Similar Cases from the Literature.

(1) The case described by De Bruyn and Stern, the pathological material from which we have been able to inspect, presents very similar features to our own. This was diagnosed as a case of hypertrophic polyneuritis of Dejerine and Sotta at the time.

A carpenter, aged 52, complained of progressive weakness with pains and numbness in the arms and legs, diarrhœa and attacks of faintness and unconsciousness. This began three years before his admission to hospital. His only previous illness had been pneumonia as a child. He was married, with two healthy children. Two brothers and one sister had died with exactly similar symptoms, weakness, diarrhœa and heart failure being the outstanding features of their terminal illnesses. In each case the symptoms lasted about three years before death.

In spite of his complaint of numbness in arms and legs, sensory changes were demonstrable only in the legs below the knees, where light touch was lost. Marked general muscular wasting was present, especially centrifugally. Coarse fibrillation was occasionally seen in both quadriceps regions. Some peripheral nerves, e.g. the ulnars and external popliteals, were readily palpable. The pupils were small and reacted poorly to light, but well on accommodation. The heart sounds were feeble, blood-pressure 95/60, and a slight secondary anæmia was present. There was hypochlorhydria. The mode of death is not described, nor is the morbid anatomy of parts other than the central nervous system.

Careful clinical extracts of many cases which had macroglossia are given in the paper by Parkes Weber and others. Of these, the following had some of the clinical features of our case.

(2) Konigstein's Case (1925). Male, aged 60, had difficulty in swallowing, macroglossia, weakness in the arms, a gradual cachexia and a nodular dermatosis. Extensive amyloid deposits were found in the whole alimentary canal at autopsy.

(3) Lubarsch's Case (1929). Male, aged 54, had an eight year's history of paralysis in various groups of muscles and digestive disturbance.

(4) Mollow and Lebell's Case (1912). Male, aged 60. Complained of abdominal pains, constipation, and enlargement of the tongue. He had trouble in walking and hypertonicity of skeletal muscles. He died of cardiac weakness.

(5) Michelson and Lynch's Case (1934). Male, aged 54, had marked weakness, pain in the lumbar region and joints, macroglossia, and Bence Jones proteinurea, swollen tender fingers, bruising with very slight trauma, skin deposits, and stubborn constipation.

Two other cases are described by Perla and Gross (1935), but not summarized by Parkes Weber.

(6) Female, aged 16. Had weakness, dyspnœa and palpitations. Her joints were sometimes red, but she had no fever. Blood-pressure 124/60. The liver was felt 4 cm. below the costal margin. Some general glandular enlargement was present. Red cells, 2·5 million; hæmoglobin, 47 per cent.; white count, normal; blood-urea, 69·2 mg. per cent., and poor urea concentration. Uræmia and chronic nephritis diagnosed. She had attacks of epistaxis and purpura in the arms, with occasional convulsions. Her blood-pressure rose to 180/94, gallop rhythm, and a pericardial rub developed terminally.

(7) Female, aged 63. Had asthenia, constipation and anorexia for two years, and then developed repeated attacks of diarrhœa with watery and bloody motions. She developed pleural effusions which were repeatedly tapped. Progressive azotæmia occurred, with vomiting and anasarca. Finally, auricular fibrillation followed an impure flutter, and she died suddenly.

(8) Larsen (1930) gives a brief clinical history of a case, male, aged 65, negro, in whom cardiac failure and œdema were the main features. He had auricular fibrillation, and the comment is made that his reflexes were sluggish or absent.

Pathological Discussion.

Primary amyloid disease has been classified by Lubarsch on an anatomical basis into three main groups:—

(1) The first is said to be characterized by involvement of tissues of mesodermal origin, such as the cardiovascular, gastro-intestinal and voluntary muscle, which show a tendency to develop nodular deposits, while the organs usually affected in the secondary form remain comparatively free.

(2) A second "tumour-forming" type consists of small, solitary or

multiple "tumours" of amyloid occurring in the eye, bladder, urethra, pharynx, tongue, skin, or in the respiratory tract.

(3) A third well-defined group appears to be associated with multiple myelomata.

The present case approximates to the first type of Lubarsch, but it also illustrates the considerable overlapping which may occur between his types. The small arteries throughout the body with the exception of those in the brain and spinal cord were affected in varying degrees, least in the lungs and liver, and most in the heart, gastro-intestinal and endocrine systems. The degree of local destruction of the parenchyma varied correspondingly.

It is generally accepted that amyloid disease begins in the small arteries and arterioles and spreads in continuity to the connective tissue, where its deposition may cause atrophy of the adjacent parenchyma, whether by pressure or vascular disturbance it has not been possible to determine. It appears to remain extra-cellular.

The origin of amyloid in both the primary and secondary forms of amyloid disease is still unknown. Chemical analysis of dried materials has been done by Eppinger (1922), who found that amyloid contained no sulphur, phosphorus or carbohydrate, but that purines and diamino acids constituted the greater part. However, the variable staining properties of amyloid point to a variability in its chemical composition, and what is recognized as amyloid histologically probably comprises a group of closely-allied substances. The amyloid in the present case exhibited the usual histological features and stained characteristically with the usual stains.

Alteration in the blood proteins, such as diminution in total serum protein, and reversal of the albumin-globulin ratio, have been described by Humphreys (1934), and has led Perla and Gross to suggest some derangement of protein metabolism as a possible cause. Since the alterations in the serum proteins may well have been due to the accompanying renal disease in the cases described, and is far from being an invariable feature of generalized amyloid, the suggestion has little to support it.

Summary.

(1) A case of primary generalized amyloid disease with involvement of the nerves is described.

(2) The muscular weakness which was a conspicuous feature of this case is attributed to amyloid infiltrations of the nerves.

(3) Attention is drawn to a clinical syndrome of muscular weakness, myocardial failure and alimentary disturbance, which is common to this case and to eight others abstracted from the literature.

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Notices of Recent Publications.

Neuro-ophthalmology. By R. Lindsay Rea. London: William Heinemann (Medical Books), Ltd. 1938. Pp. 568. Price 42s.

The author has written an exhaustive account of the ophthalmic aspect and associations of diseases of the nervous system, including under the latter heading the psychoneuroses. The task is necessarily an ambitious one for the ophthalmic surgeon, for it covers a wide range of pathological and clinical knowledge, with much of which he can have little but a literary acquaintance.

The chief difficulty, perhaps, which besets an author in these circumstances is that of assessing the value and significance of all that part of his subject with which he has not a first-hand clinical experience. The critical faculty cannot adequately do its work where this experience fails. Here and there in the present book is evidence of this difficulty, shown as statements and judgments that the experienced neurologist would not have made. Thus disseminated sclerosis is baldly classed with tabes dorsalis as "infections of the nervous system," a statement which is later qualified. The optic atrophy of tabes is said "often" to precede other signs of this malady. Nystagmus is said to be "commonly" present in subacute combined degeneration of the cord, and the discovery of the association of this malady with pernicious anæmia is attributed to a modern source very many years later than it was actually made. Finally, it is premature to say that "progress has reached the stage when the location of tumours of the brain may be discovered by the electro-encephalogram."

Very many nervous diseases which have no significant ophthalmological signs are given scrappy paragraphs, too brief to be of value and lacking the balance and accuracy that are necessary to gain the reader's confidence.

The chapter dealing with the psychoneuroses attempts within a page or two to discuss the various hypotheses which compete for acceptance as to the genesis of these disorders, a topic not within the compass of the book's title, and not adding to its value.

These few examples will serve to indicate that the author has perhaps cast his net too wide, and would better have served his readers had he been more modest in his aims.

Nevertheless, on the more strictly ophthalmological side of the book, he writes clearly and with authority and has provided the ophthalmologist with a useful compilation of the neurology of the eye.

The book is excellently produced, has an exhaustive bibliography, and is well illustrated.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By F. R. FORD. London: Baillière, Tindall and Cox. 1937. Pp. 953. Price 38s.

No more comprehensive or valuable addition to the ranks of neurological textbooks than Dr. Ford's has appeared in the English language for some considerable time. It forms a work of reference without which no neurologist's library will be complete. It includes succinct and extremely clear sections upon every recorded affection of the neuromuscular system within the age period with which it deals. These accounts are admirably balanced, and each section is followed by an adequate and representative bibliography.

It opens with the usual chapters upon clinical methods of examination and upon the essentials of nervous anatomy and physiology. The classification is unusual but practical, and consists of chapters on prenatal diseases, heredofamilial and congenital diseases, infections and parasitic diseases, toxic and metabolic disorders, vascular and circulatory disorders, neoplasms, injuries, diseases of the autonomic system, muscular diseases, and a final chapter devoted to symptom-complexes.

The illustrations and diagrams are original, well chosen and well produced.

The book really deals with more than diseases peculiar to the pre-adult period of life and it is in fact a textbook of neurology. A series of typical case reports illustrate the various conditions described. It is to be hoped that in future editions the index may be improved. It is incomplete and contains numerous misspellings.

Die Kuppelungen von Pupillenstörungen mit Aufhebung der Sehnenreflexe. By VON F. KEHRER. Leipzig: Georg Thieme. 1937. S.60. Price 6M.

The author reviews in some detail all the published works on the subject of the tonic pupil, gives minute descriptions and classifications of the clinical variants, and of the pupillary anomalies that may have to be differentiated from the syndrome he is dealing with.

The monograph is mainly descriptive and no fresh generalizations emerge, but it is a useful résumé of the present state of knowledge upon its subject. Several important papers that are freely referred to in the text find no place in the bibliography, and no reference is given to the journals in which they appeared.

Children Handicapped by Cerebral Palsy: Psychological factors in management. By ELIZABETH E. LORD, with a medical explanation by B. CROTHERS. New York: The Commonwealth Fund. London: Oxford University Press. 1937. Pp. 102. Price 5s. 6d.

This valuable little book deals with the care, management and training of a class of chronic sufferers for whom in the past little beyond crude orthopædic

procedures have been attempted. It should be studied by all who may have to advise upon the training of the diplegic child, by all who may have to undertake or supervise this training, and there are some mothers into whose hands it might be put with advantage.

The assessment of mental and physical condition and potentialities is described, and its bearing upon the plan of treatment to be adopted. This plan embraces the various aspects of the child's training and education, and due stress is laid upon the necessity of trying to make the situation to be dealt with clear to the child's parents, and of securing, when possible, their intelligent co-operation.

Neurology. By R. GRINKER. Second Edition. London: Baillière, Tindall and Cox. 1937. Pp. 1,000. Price 38s.

In the preface to this edition the author refers to the difficulty of avoiding the progressive enlargement of a textbook, and to the changes involved in deleting matter that has not stood the test of time since the appearance of the first edition.

To-day, perhaps, the chief art in the writing of a textbook is not in the inclusion of all that has been said on its subject, but in the exclusion of what has not in some measure already stood the test of time. A textbook is scarcely the place in which the merely hypothetical or the uncorroborated should appear. For these the original paper and the critical review are the appropriate media.

Difficulties must also beset the endeavour to do justice to recent advances and changes of opinion in anatomy and physiology as well as to clinical neurology and neuropathology within the bounds of a single volume, and the attempt to do so often leads to an overloading with the former at the expense of the latter. Thus the proportions desirable in a work for clinicians are lost.

In the present edition just over a quarter of the matter is devoted to anatomy and physiology, including recent additions to knowledge that have yet to find a clinical application, or indeed any application to the human subject. Approximately twice as much space is given to the anatomy and physiology of the cerebellum as to its diseases and their symptoms and pathology, while the cyto-architectonics of the cerebral cortex occupy as many pages as are devoted to multiple peripheral neuritis. Indeed, the purely clinical sections of the book are not on the same scale of comprehensiveness as those given to the ancillary sciences.

In the matter of clinical description, such a progressive malady of the nervous system as disseminated sclerosis, for example, may be regarded as a sequence of events, this sequence being the natural history of the malady. To obtain the story of his illness from the patient, and to assess the significance of his symptoms and physical signs demand of the investigator a knowledge of this natural history, and it is one of the first functions of a textbook to provide this. Mere disjointed paragraphs describing—in no matter what detail—the separate components of the clinical picture do not give this vivid sense of an active process.

To provide such a continuous story undoubtedly calls for a ripe clinical experience and a modest measure of literary skill, but it is the vivid accounts of disease given by the authors of a past generation—as those acquainted with Gowers' famous textbook will acknowledge—that made their books, and still make them, so full of life and so delightful to read. Without this element no textbook can hope to reach the first rank.

In the independence and freshness of his thought and the clarity of his expression the author has shown his ability to provide this, and it may be hoped that in the further editions of his work that will be called for, he may find it expedient to alter somewhat the balance of his material. The first approach of the clinician to nervous disease is by simple observation at the bedside and the fullest aids to this should be given him. If economies of space are called for, they should not be made at the expense of clinical medicine.

With these reservations, the book may be recommended to the student of neurology as a lucid exposition of modern neurological knowledge.

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